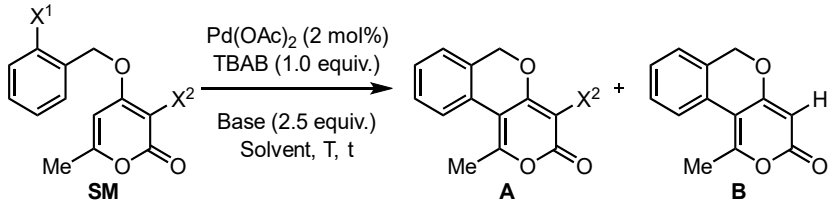
Table of Contents

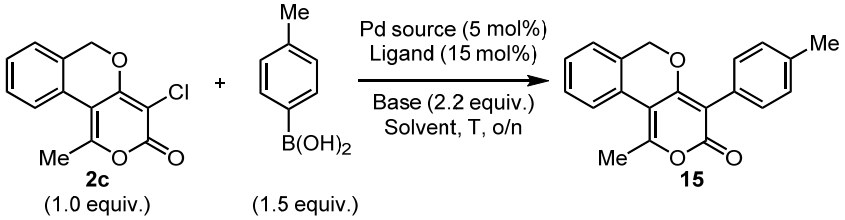
Table S1. Optimisation of the Direct Arylation Reaction



X^1	X^2	TBAB	Base	Solvent	T (°C)	Time (h)	Product[a)]
I	I	1.0	KOAc	DMF	100	4.5	degradation
I	Br	1.0	KOAc	DMF	100	6	**B** (90%)
I	Br	1.0	KOAc	Toluene	127	4	**B**
I	Br	1.0	KOAc	THF	76	6	**B**
Br	Br	1.0	KOAc	DMF	100	4.5	**B** (78%)
Br	I	1.0	KOAc	DMF	100	4	**A** (11%) **B** (5%)
Br	Cl	1.0	KOAc	THF	76	8	**SM:A**[b)] 61:39
I	Cl	1.0	Na_2CO_3	THF	76	8	mixture
I	Cl	0.5	KOAc	THF	76	8	**SM**
I	Cl	0.2	KOAc	THF	76	8	**SM**
I	Cl	–	Na_2CO_3 [c)]	NMP	60	16	**A** 40%

[a)] Isolated yields. Yields calculated using quantitative ^{1}H NMR in parenthesis. [b)] Conversion calculated from the ^{1}H NMR spectrum of the crude reaction mixture. [c)] Reaction conditions: $Pd_2(dba)_3$ (2 mol%), PPh_3 (4 mol%), PivOH (30 mol%), Na_2CO_3 (3.0 equiv.).

Table S2. Optimisation of the Suzuki-Miyaura Cross-Coupling Reaction



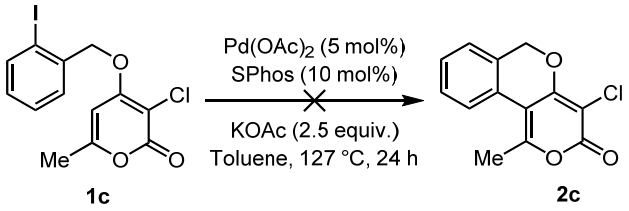
Pd Source	Ligand	Base	Solvent	T (°C)	Conversion[a)]
$Pd_2(dba)_3$ (1.5 mol%)	$P(^tBu)_3.HBF_4$ (3.6 mol%)	KF (3.3 equiv.)	THF	60	0
$Pd(OAc)_2$ (2 mol%)	DavePhos (3 mol%)	CsF (3.0 equiv.)	Dioxane	110	0
$Pd(OAc)_2$	SPhos[b)]	K_2CO_3	Toluene	110	60
$Pd(OAc)_2$	SPhos[b)]	Cs_2CO_3	Toluene	110	degradation
$Pd(OAc)_2$	SPhos[b)]	KOAc	Toluene	110	70
$Pd(OAc)_2$	SPhos[b)]	KOAc	Toluene	127	22
$Pd(OAc)_2$	SPhos[b)]	KOAc	THF	76	71
$Pd(OAc)_2$	XPhos	KOAc	THF	76	29
$Pd(OAc)_2$	RuPhos	KOAc	THF	76	64
$Pd_2(dba)_3$	SPhos	KOAc	THF	76	6
$Pd(OAc)_2$	SPhos	KOAc	2-MeTHF	90	69
$Pd(OAc)_2$	SPhos	KOAc	1,4-Dioxane	110	44
$Pd(OAc)_2$	SPhos	KOAc	THF	50	9
$Pd(OAc)_2$	SPhos	KOAc	THF	76	93 (92)

[a)] Conversion calculated from the ^1H NMR spectrum of the crude reaction mixture. Isolated yields in parenthesis. [b)] 10 mol%.

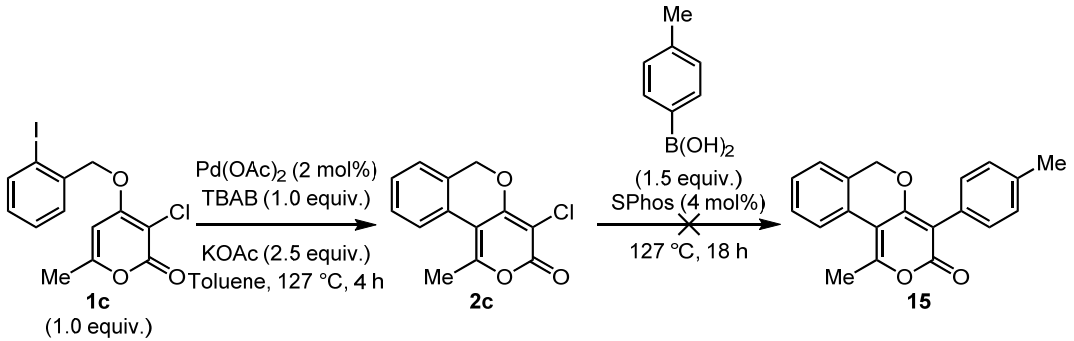
Investigation of a one-pot direct arylation/Suzuki-Miyaura cross-coupling

It was anticipated that due to the similarity of the reaction conditions ($Pd(OAc)_2$, KOAc, THF, 76 °C), a one pot direct arylation/Suzuki-Miyaura cross-coupling could be performed on these substrates. Unfortunately, all attempts to do so were unsuccessful. In summary:

The Suzuki-Miyaura conditions do not catalyse the direct arylation reaction.



It was also attempted to add in the SPhos ligand and boronic acid after the direct arylation reaction had proceeded to completion, but this was also unsuccessful at providing the final product.

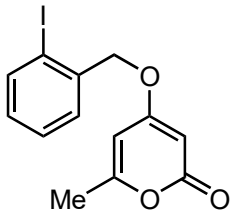


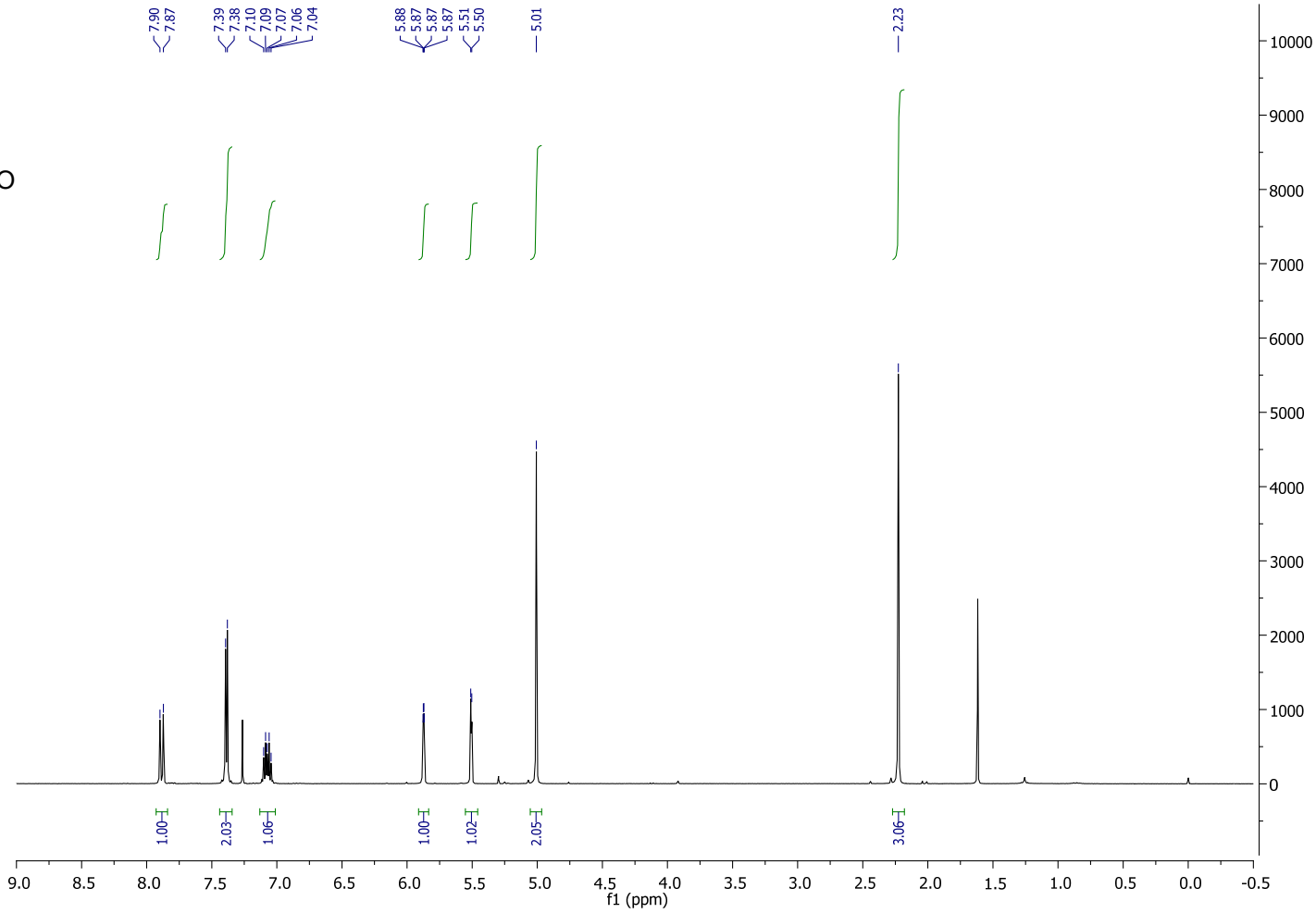
This demonstrates the difficulty in using one precatalyst for two mechanistically distinct transformations, and the exquisitely precise conditions which are required for each transformation.

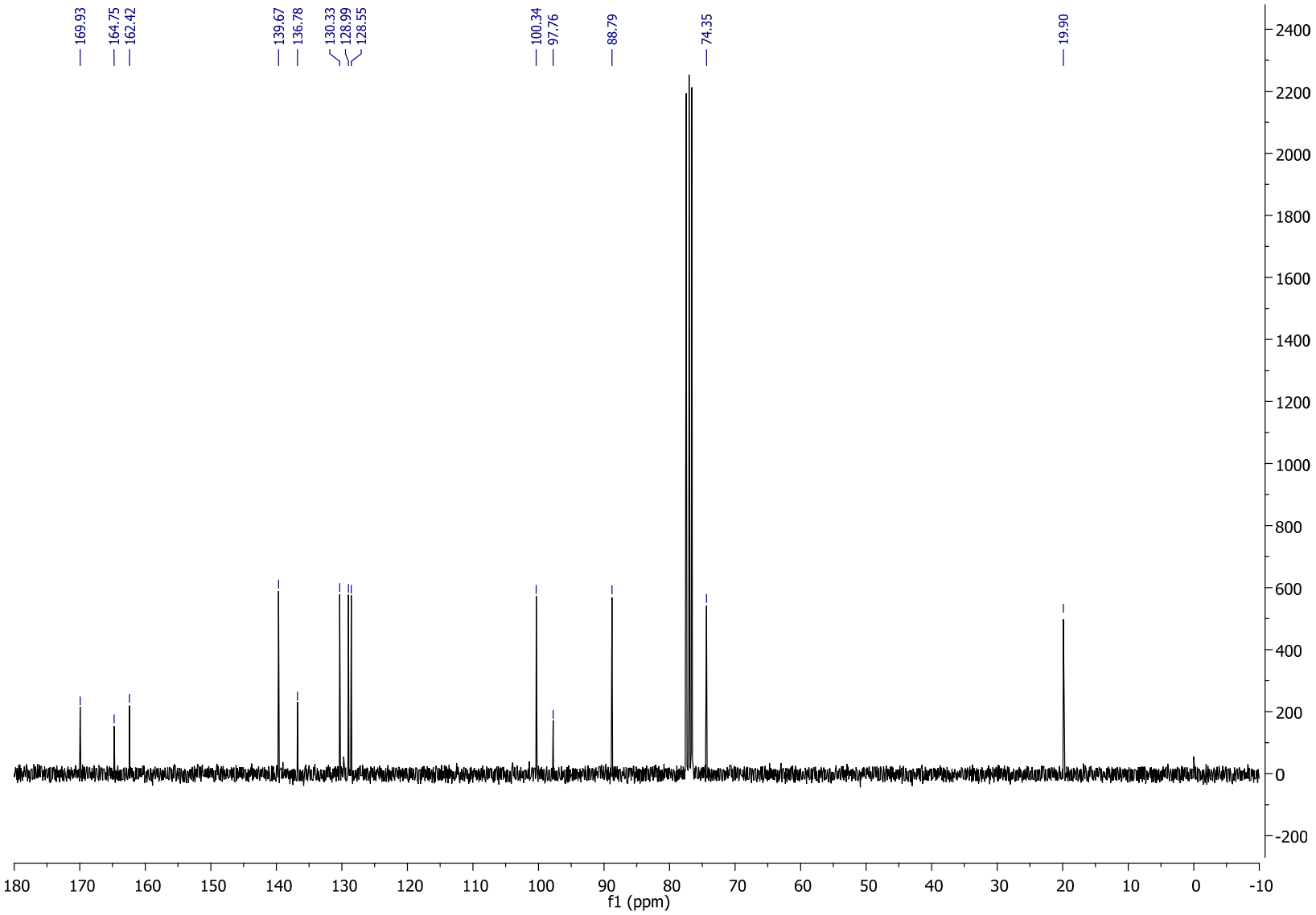
Spectra

4-Benzyloxy-2-pyrones and 2-pyridones

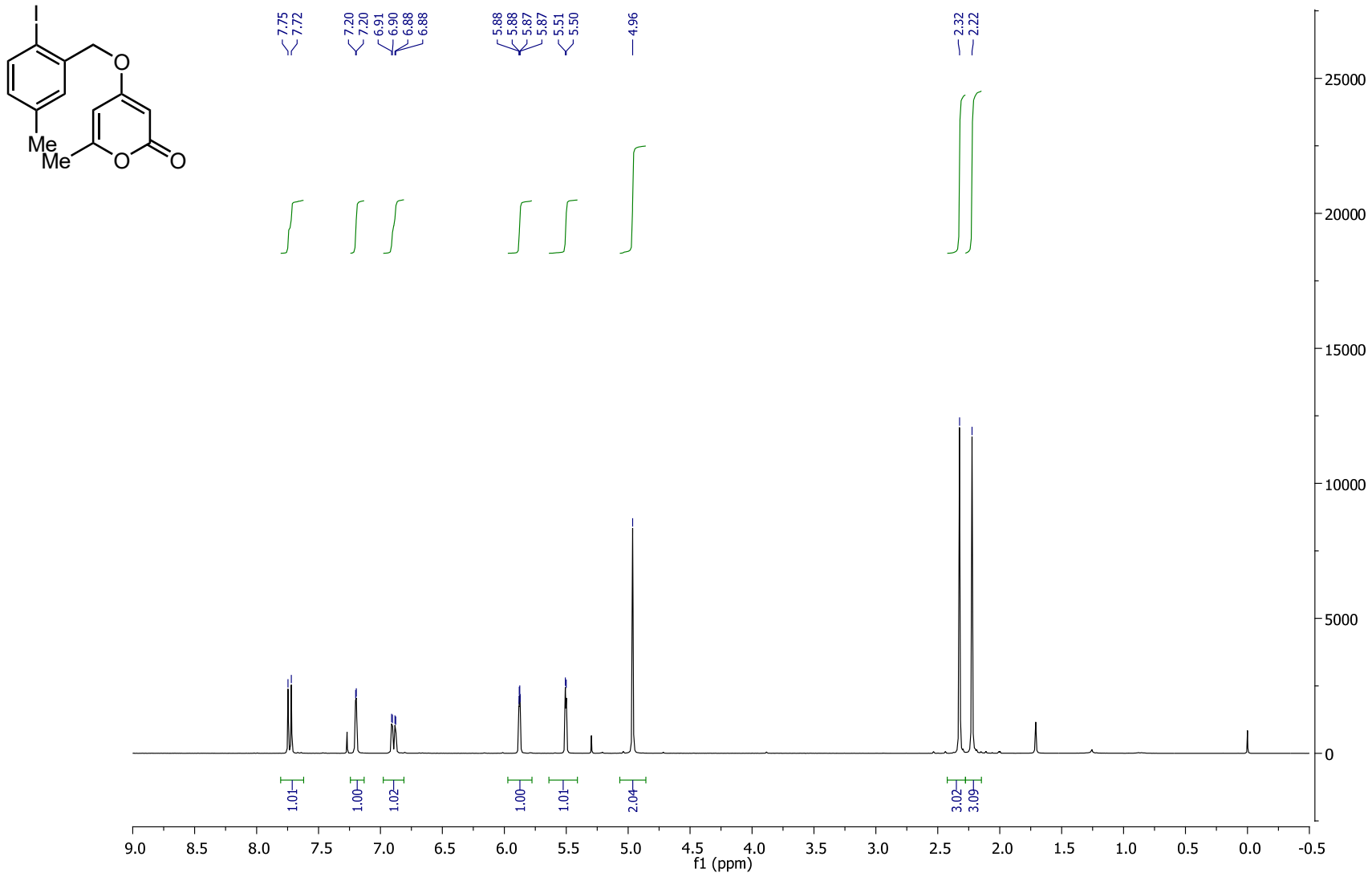
4-((2-Iodobenzyl)oxy)-6-methyl-2*H*-pyran-2-one

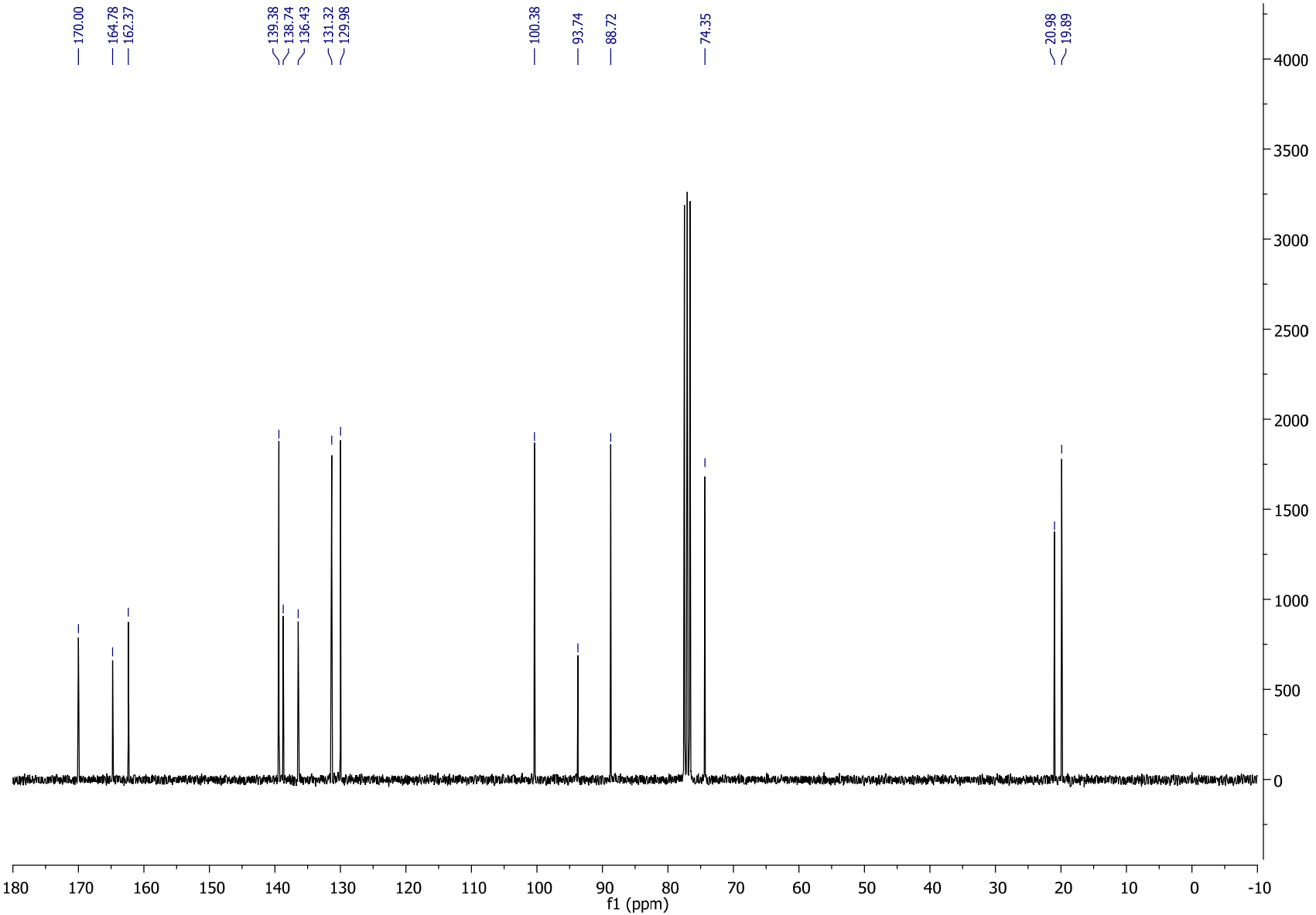




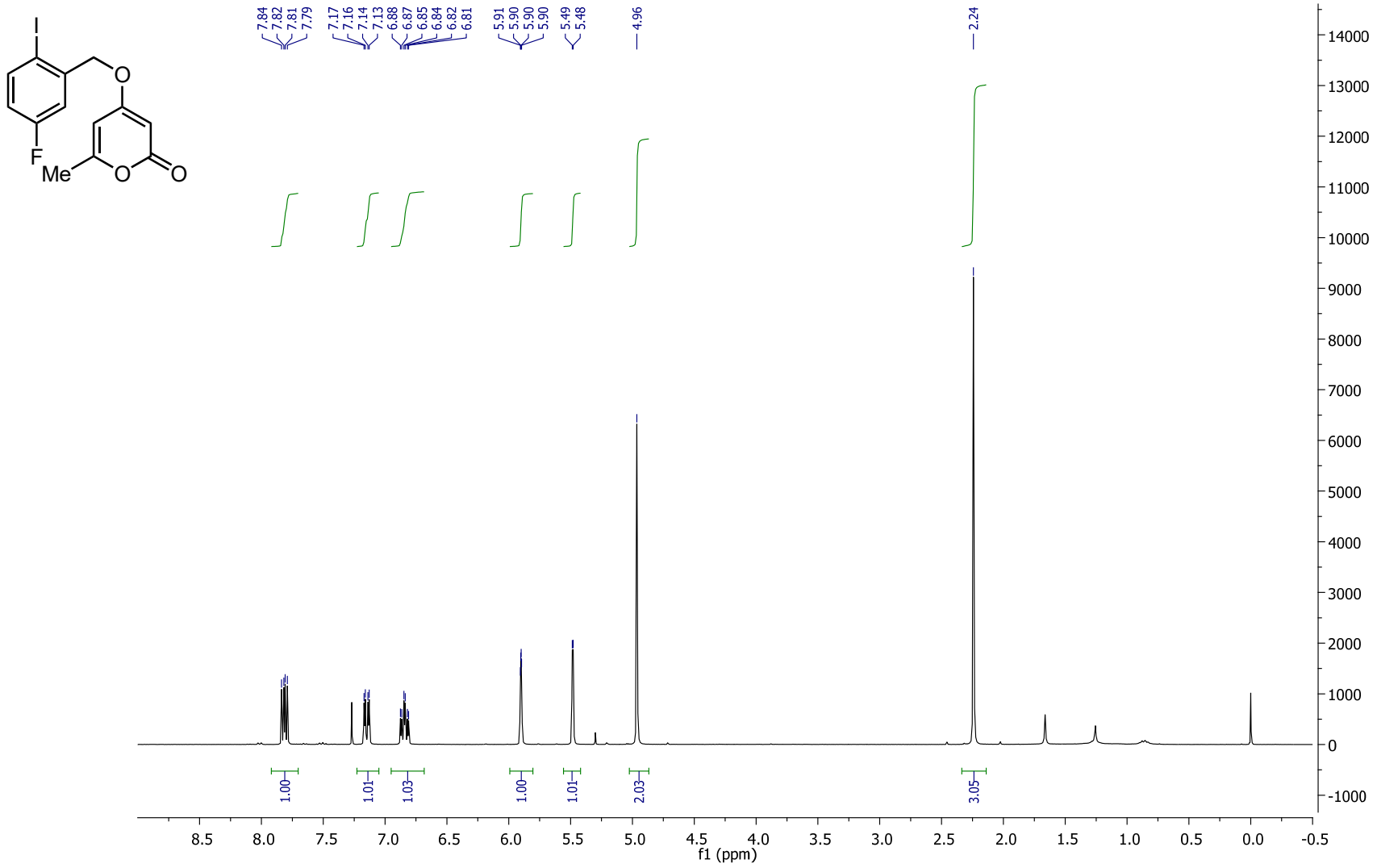

169.93
164.75
162.42
139.67
136.78
130.33
128.99
128.55
100.34
97.76
88.79
74.35
19.90
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

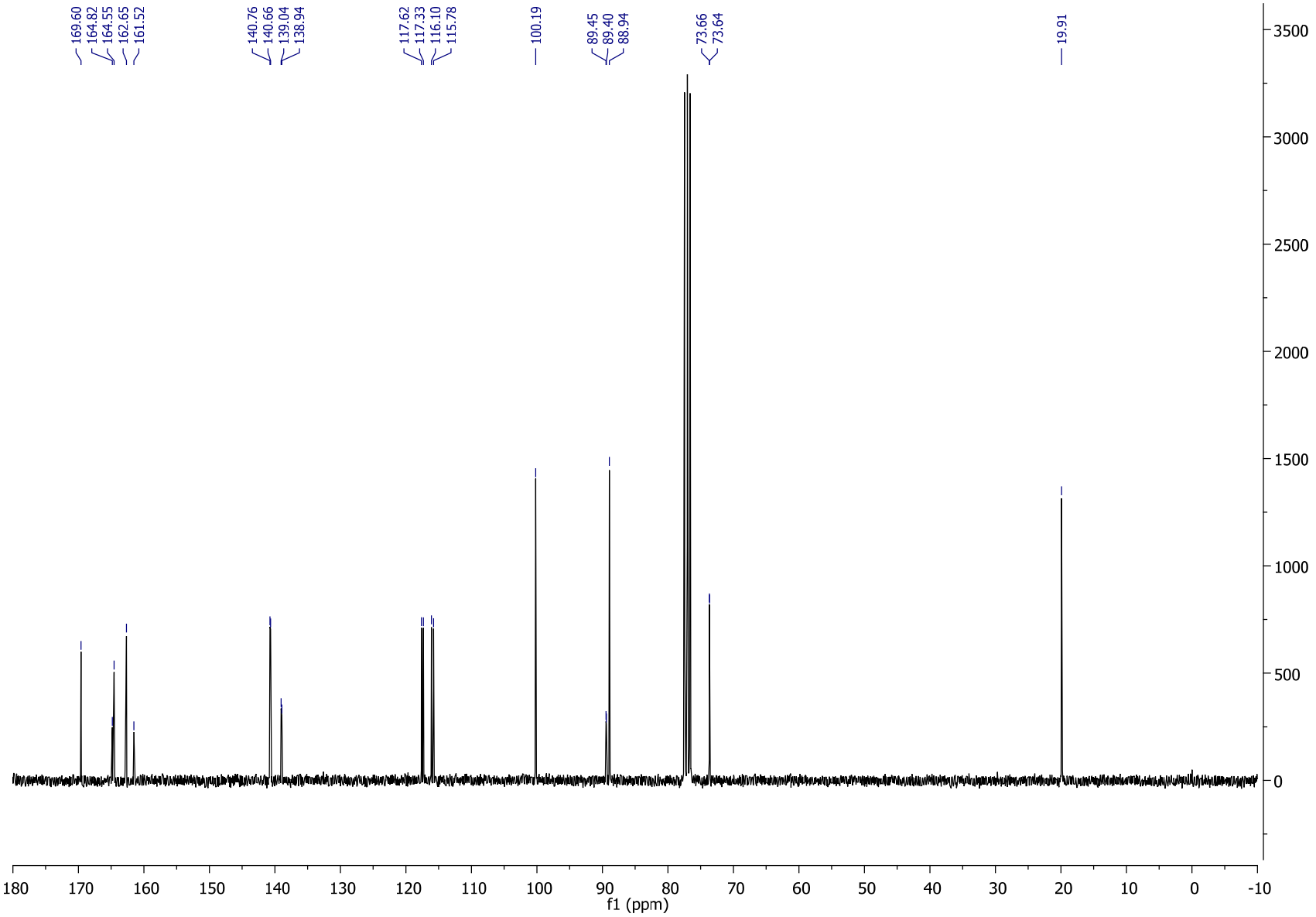
4-((2-Iodo-5-methylbenzyl)oxy)-6-methyl-2*H*-pyran-2-one

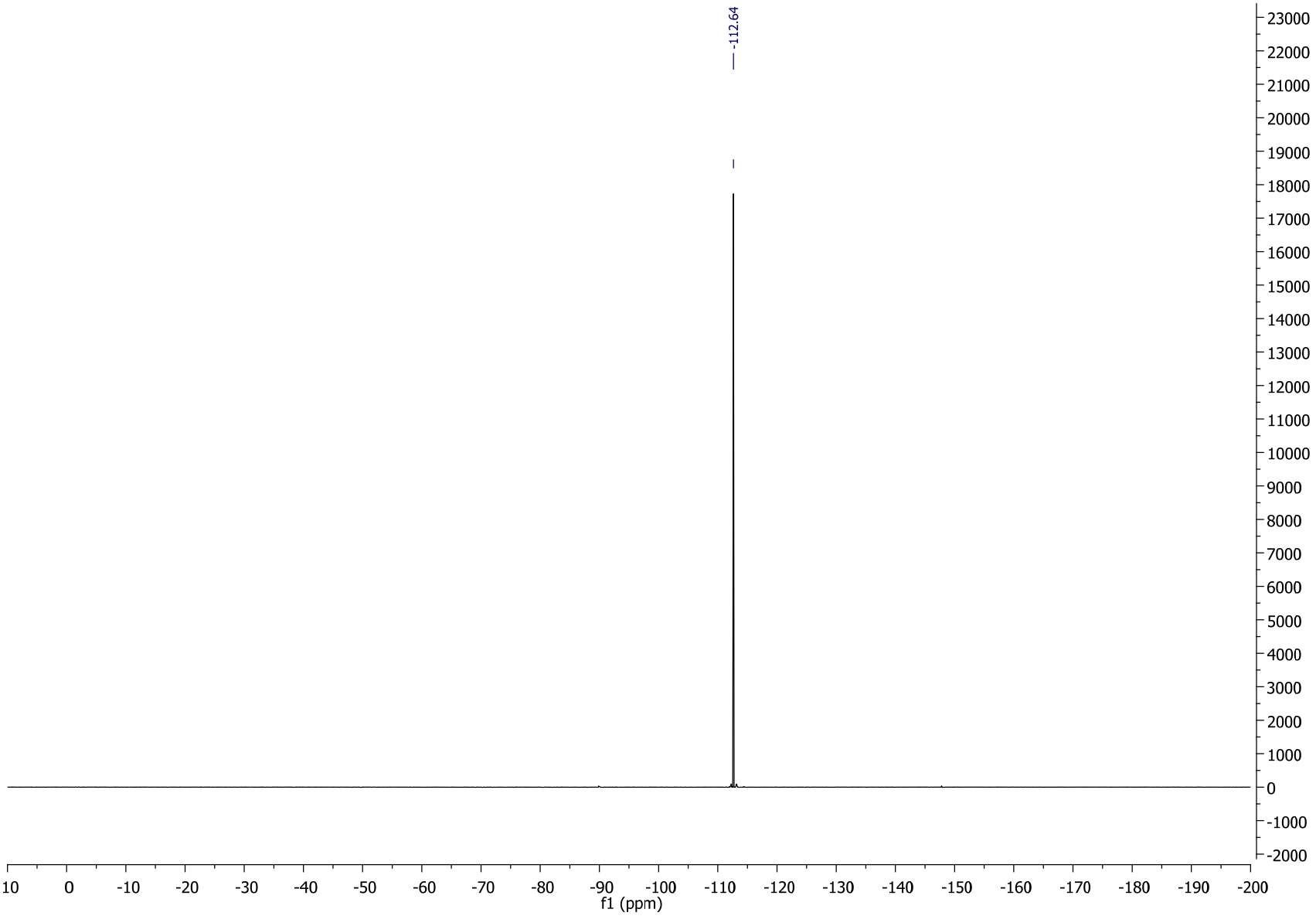



170.00
164.78
162.37
139.38
138.74
136.43
131.32
129.98
100.38
93.74
88.72
74.35
20.98
19.89
4000
3500
3000
2500
2000
1500
1000
500
0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

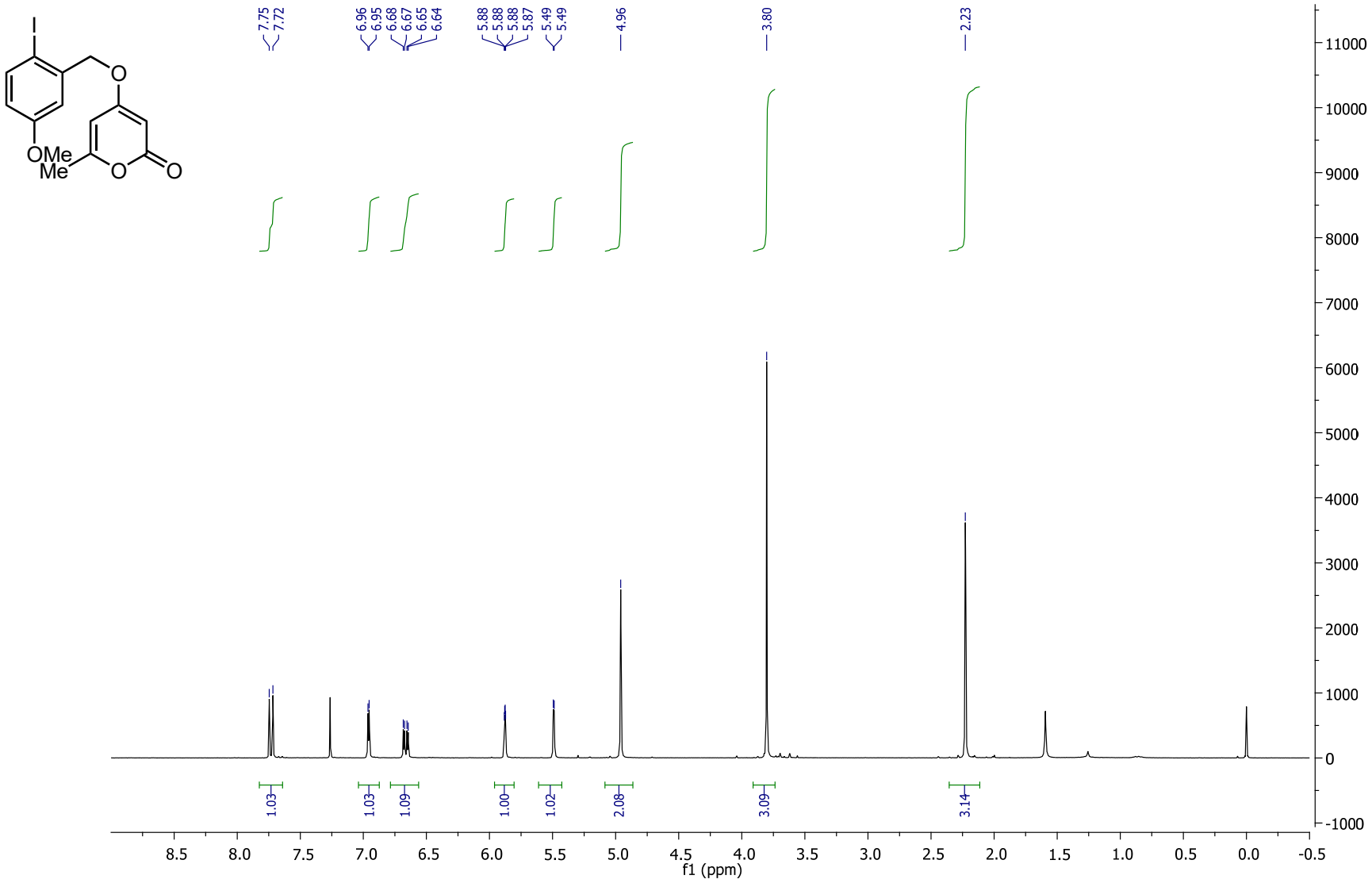
4-((5-Fluoro-2-iodobenzyl)oxy)-6-methyl-2*H*-pyran-2-one

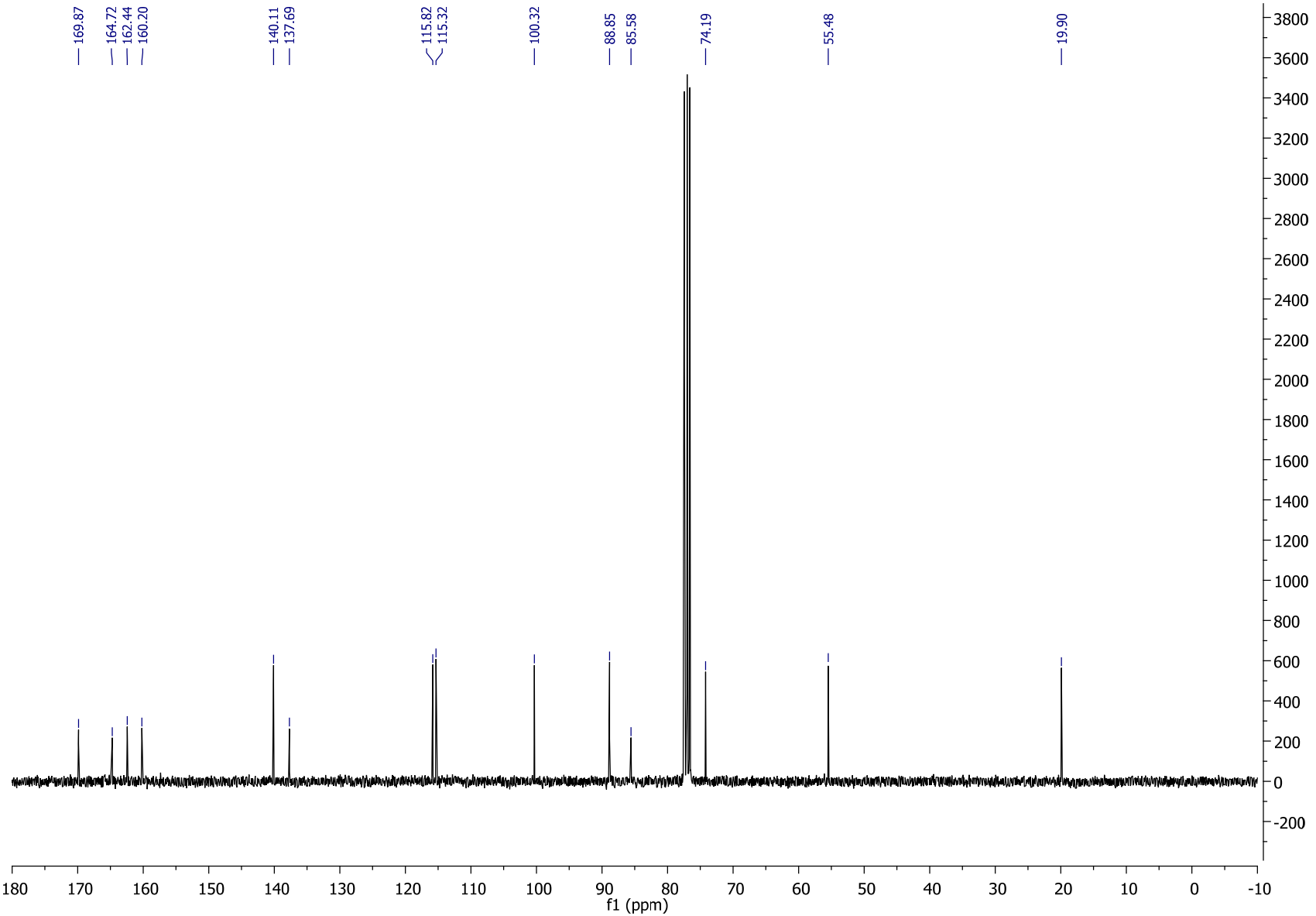



169.60
164.82
164.55
162.65
161.52
140.76
140.66
139.04
138.94
117.62
117.33
116.10
115.78
100.19
89.45
89.40
88.94
73.66
73.64
19.91
3500
3000
2500
2000
1500
1000
500
0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

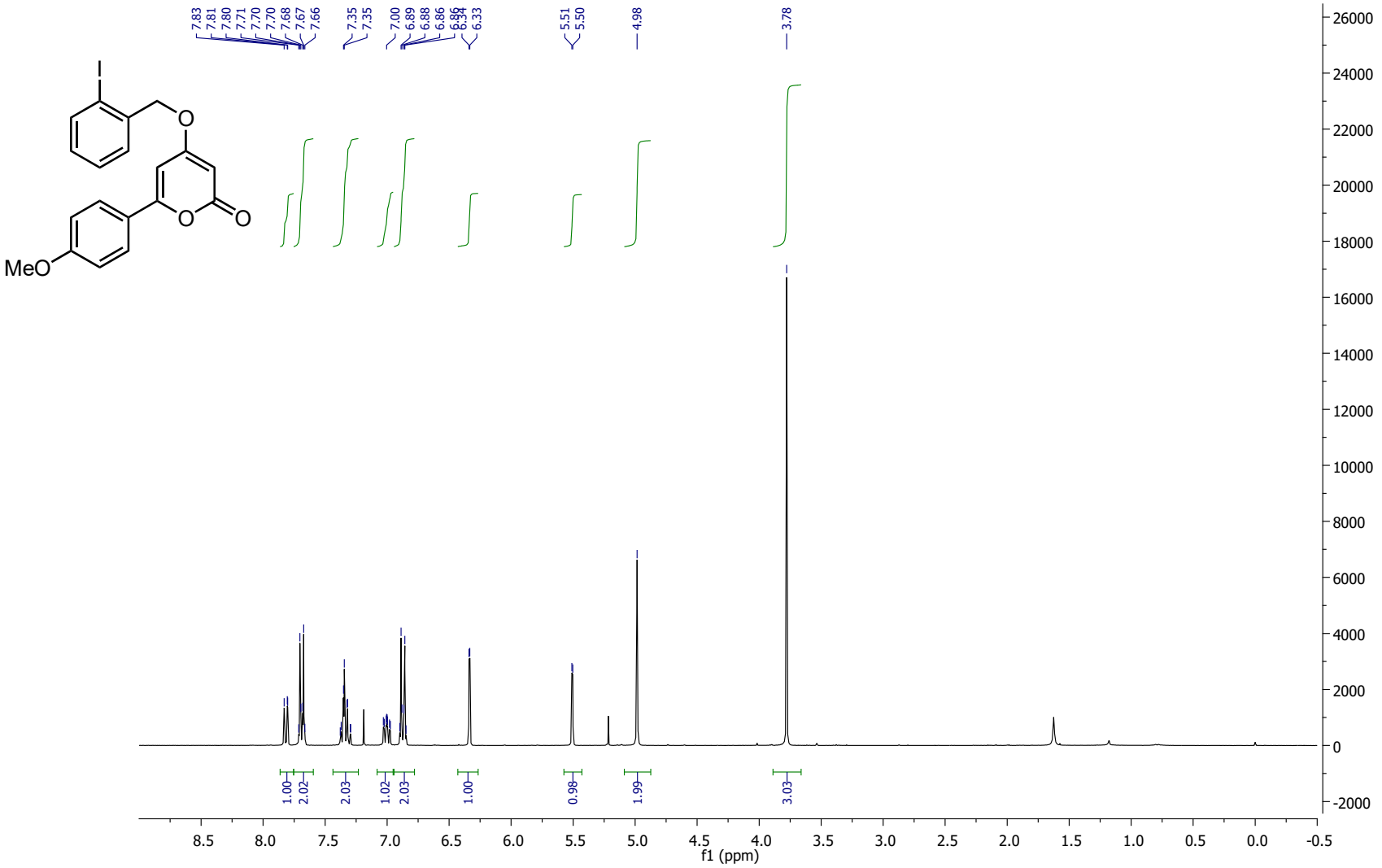

-112.64
23000
22000
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

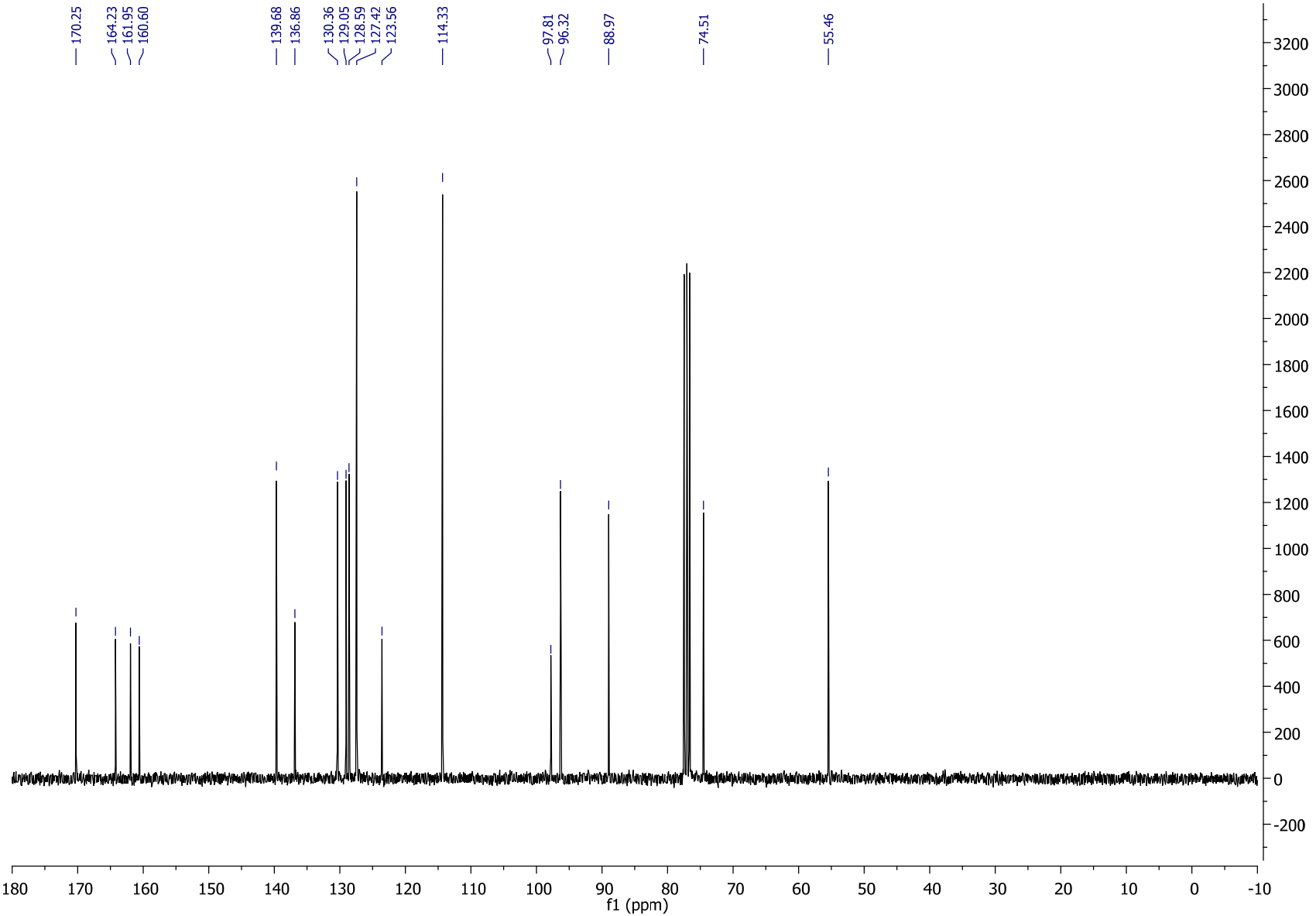
4-((2-Iodo-5-methoxybenzyl)oxy)-6-methyl-2*H*-pyran-2-one



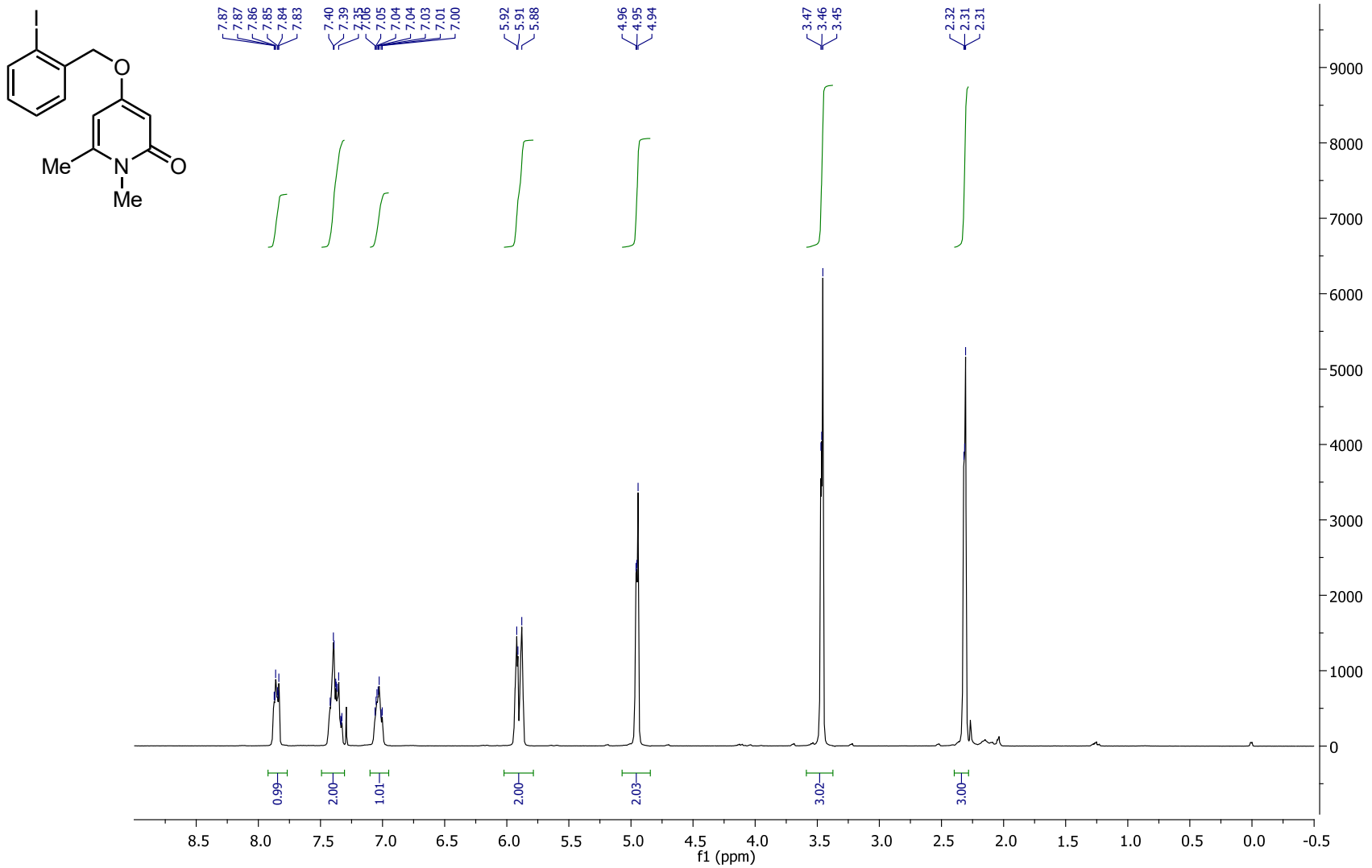

169.87
164.72
162.44
160.20
140.11
137.69
115.82
115.32
100.32
88.85
85.58
74.19
55.48
19.90
f1 (ppm)

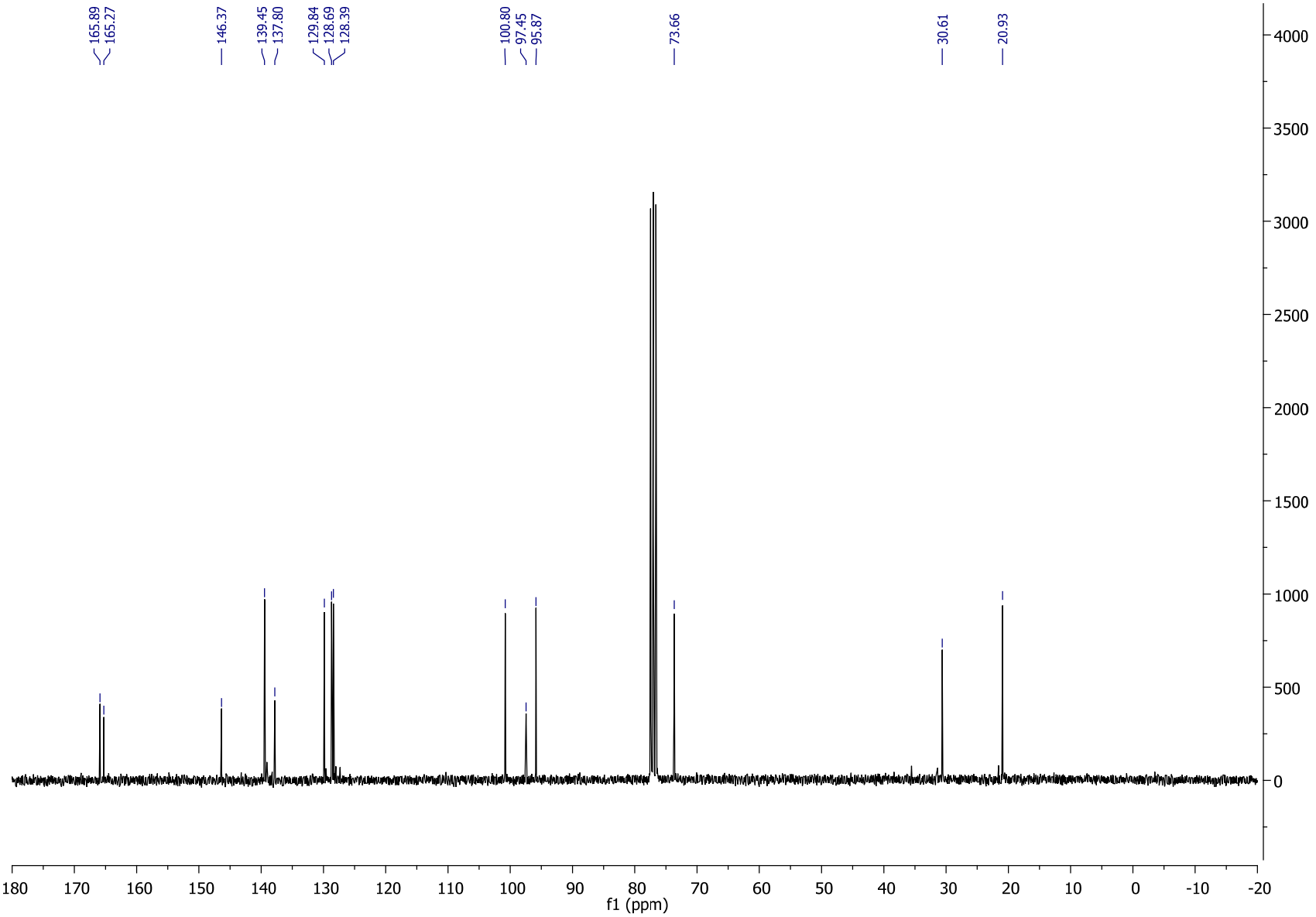
4-((2-Iodobenzyl)oxy)-6-(4-methoxyphenyl)-2*H*-pyran-2-one



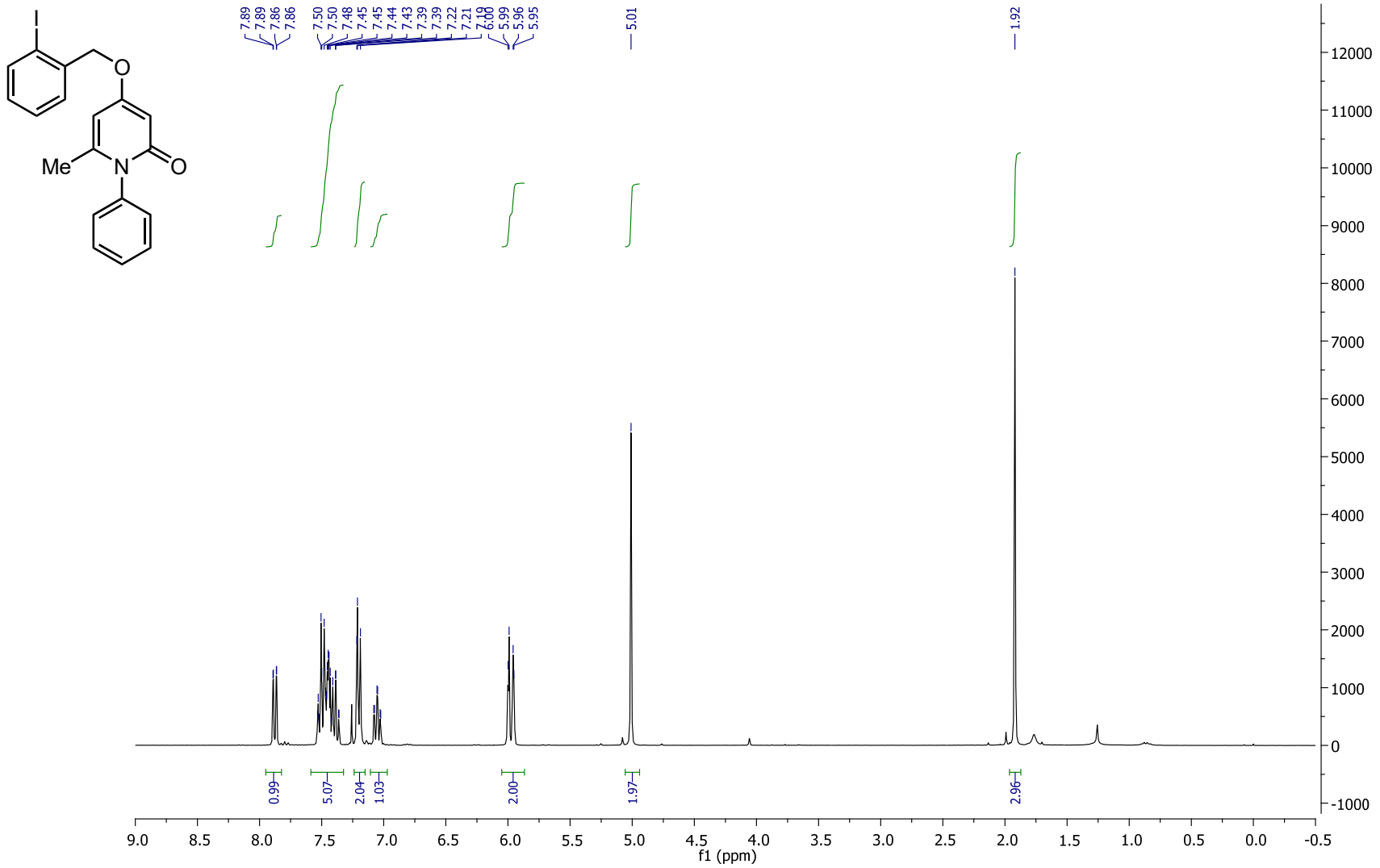

170.25
164.23
161.95
160.60
139.68
136.86
130.36
129.05
128.59
127.42
123.56
114.33
97.81
96.32
88.97
74.51
55.46
f1 (ppm)

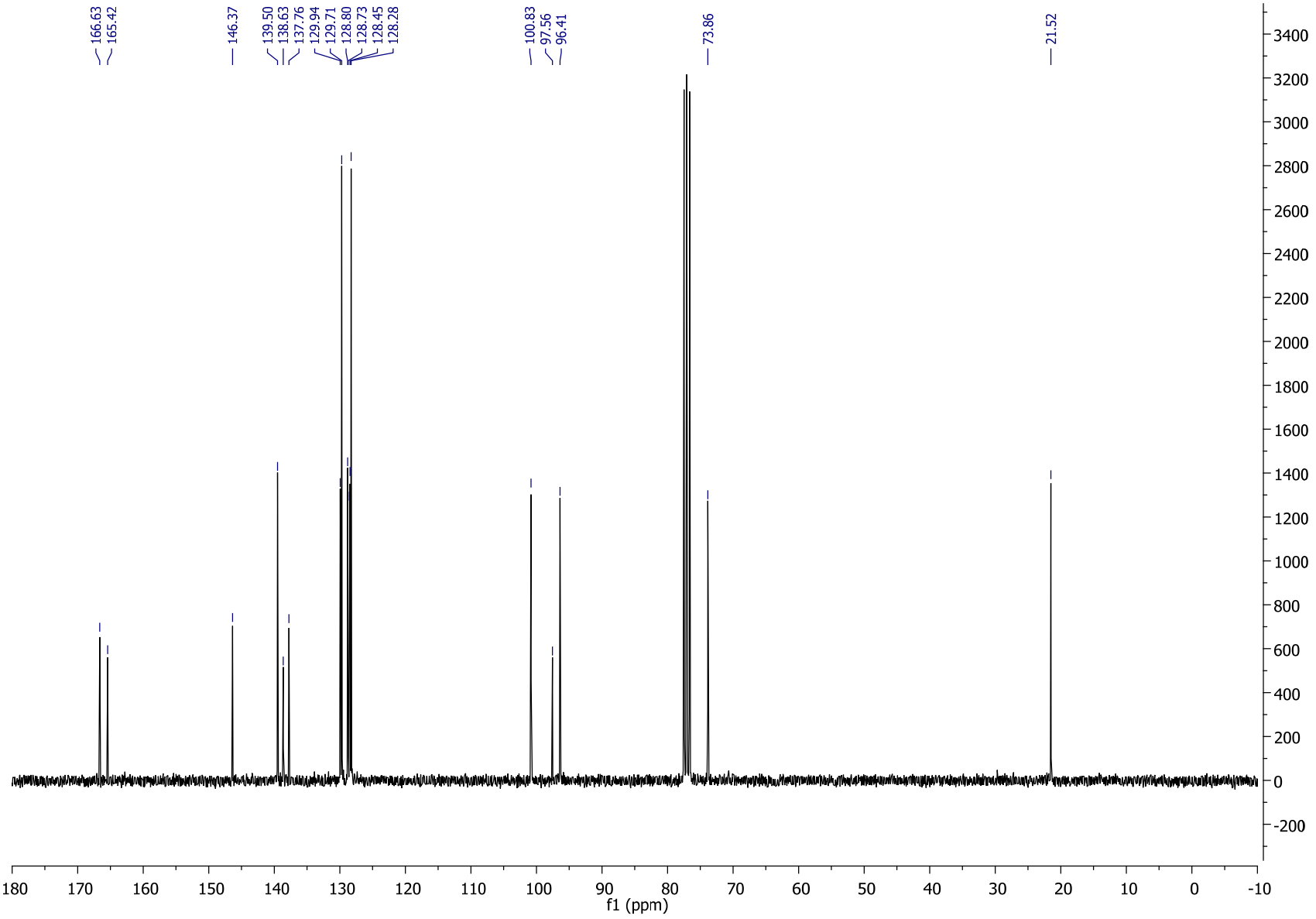
4-((2-Iodobenzyl)oxy)-1,6-dimethylpyridin-2(1*H*)-one




165.89
165.27
146.37
139.45
137.80
129.84
128.69
128.39
100.80
97.45
95.87
73.66
30.61
20.93
4000
3500
3000
2500
2000
1500
1000
500
0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

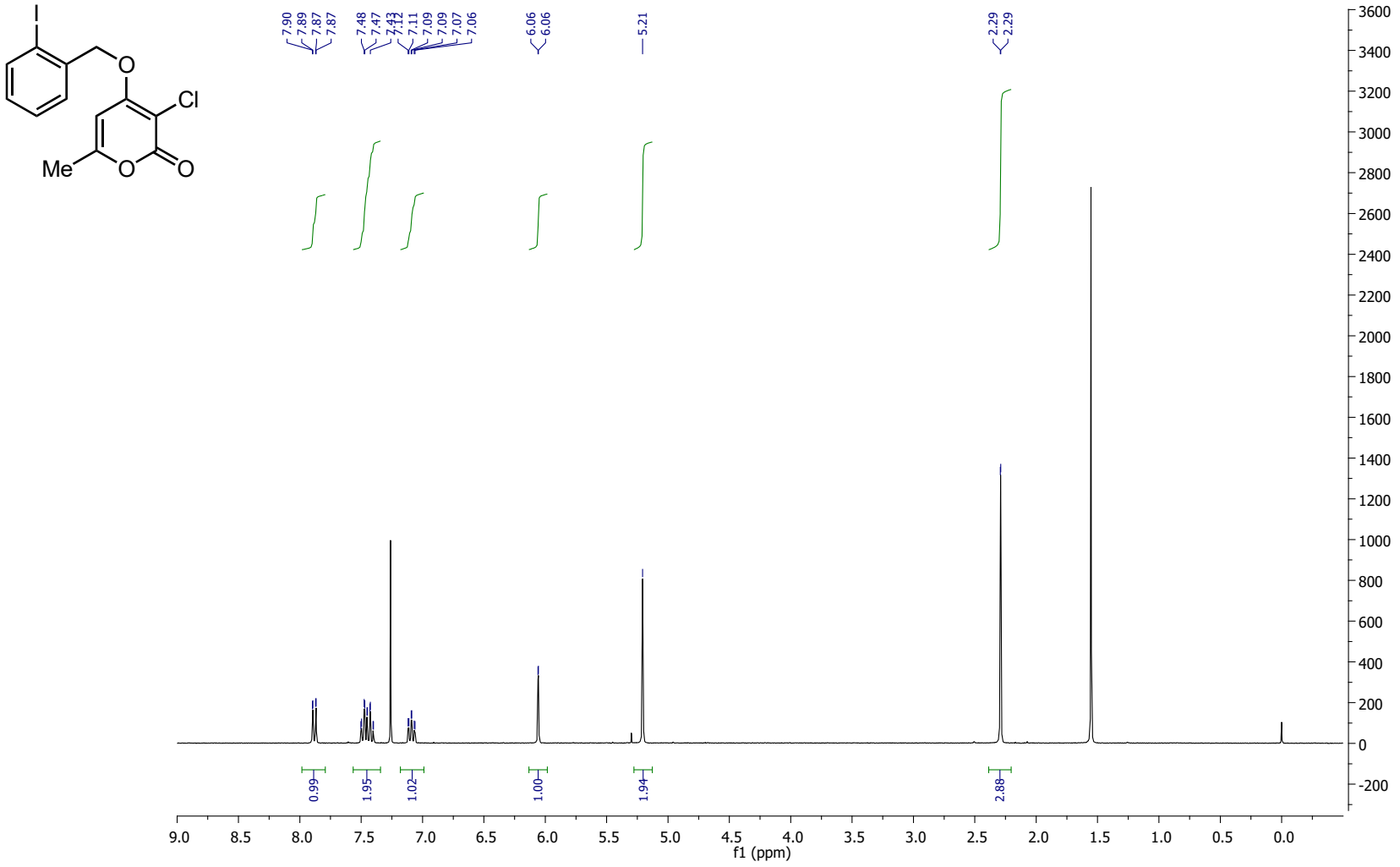
4-((2-Iodobenzyl)oxy)-6-methyl-1-phenylpyridin-2(1*H*)-one

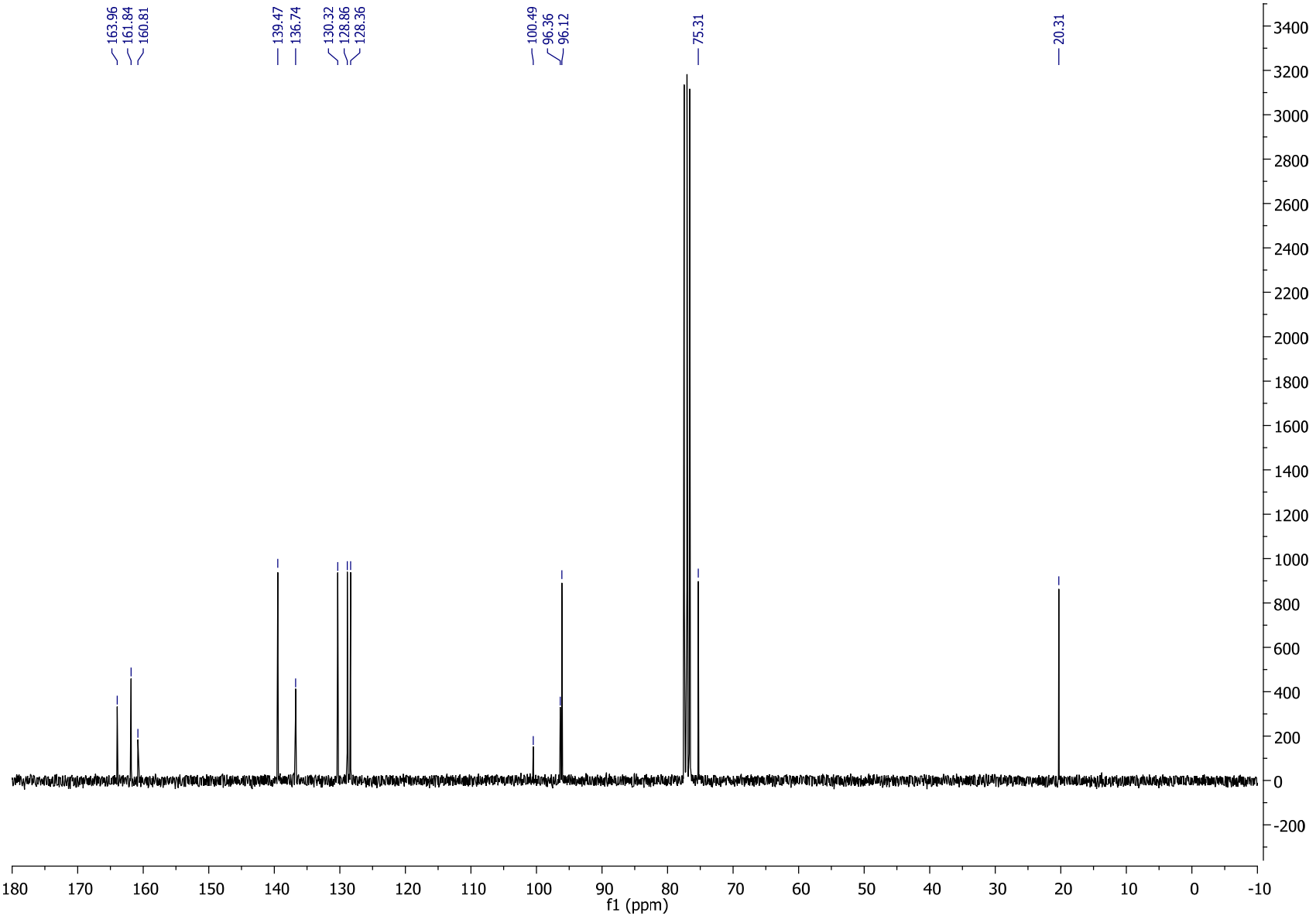



166.63
165.42
146.37
139.50
138.63
137.76
129.94
129.71
128.80
128.73
128.45
128.28
100.83
97.56
96.41
73.86
21.52
f1 (ppm)

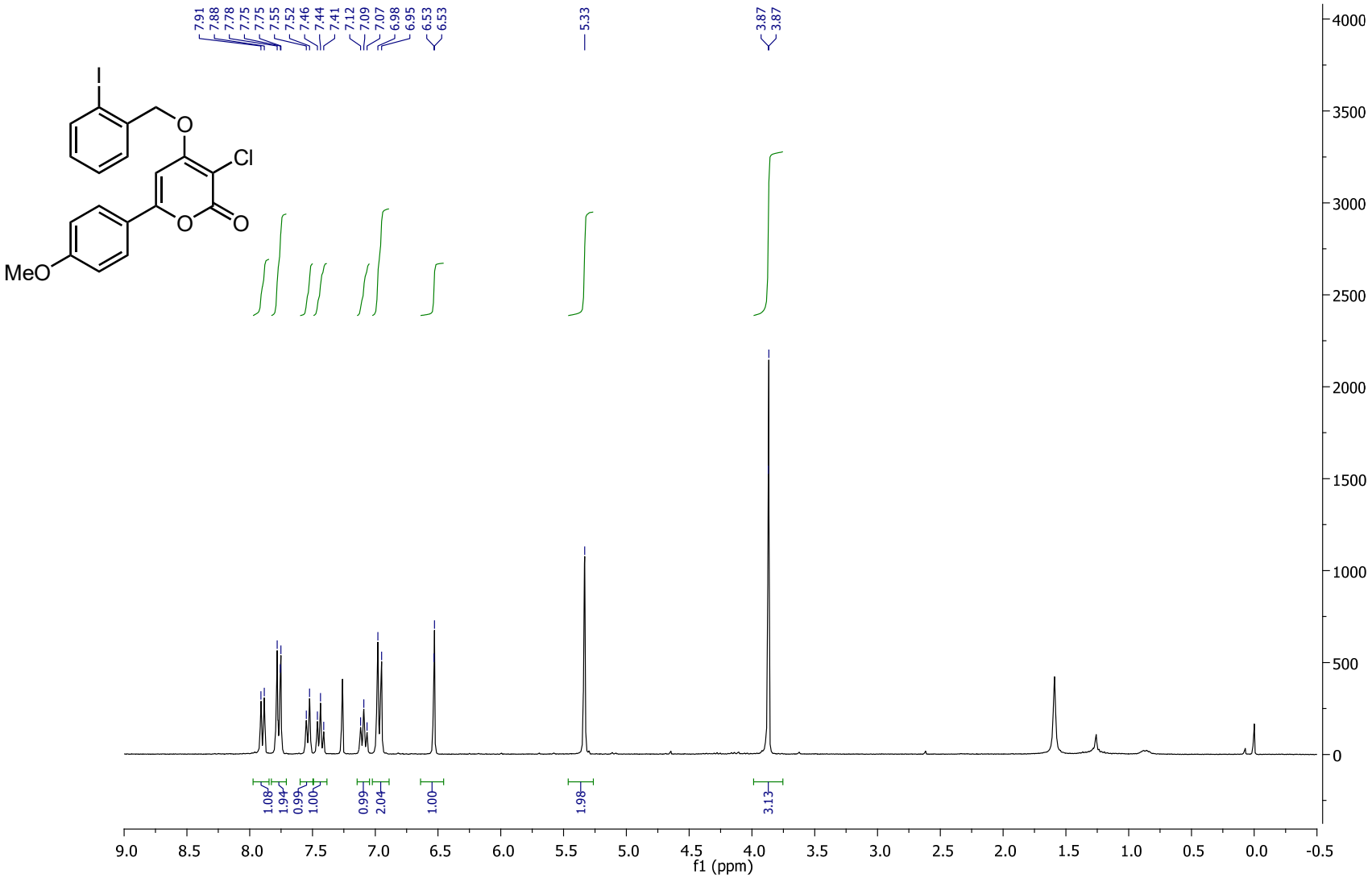
3-Chloro-4-benzyloxy-2-pyrones and 2-pyridones (1c, 3-8)

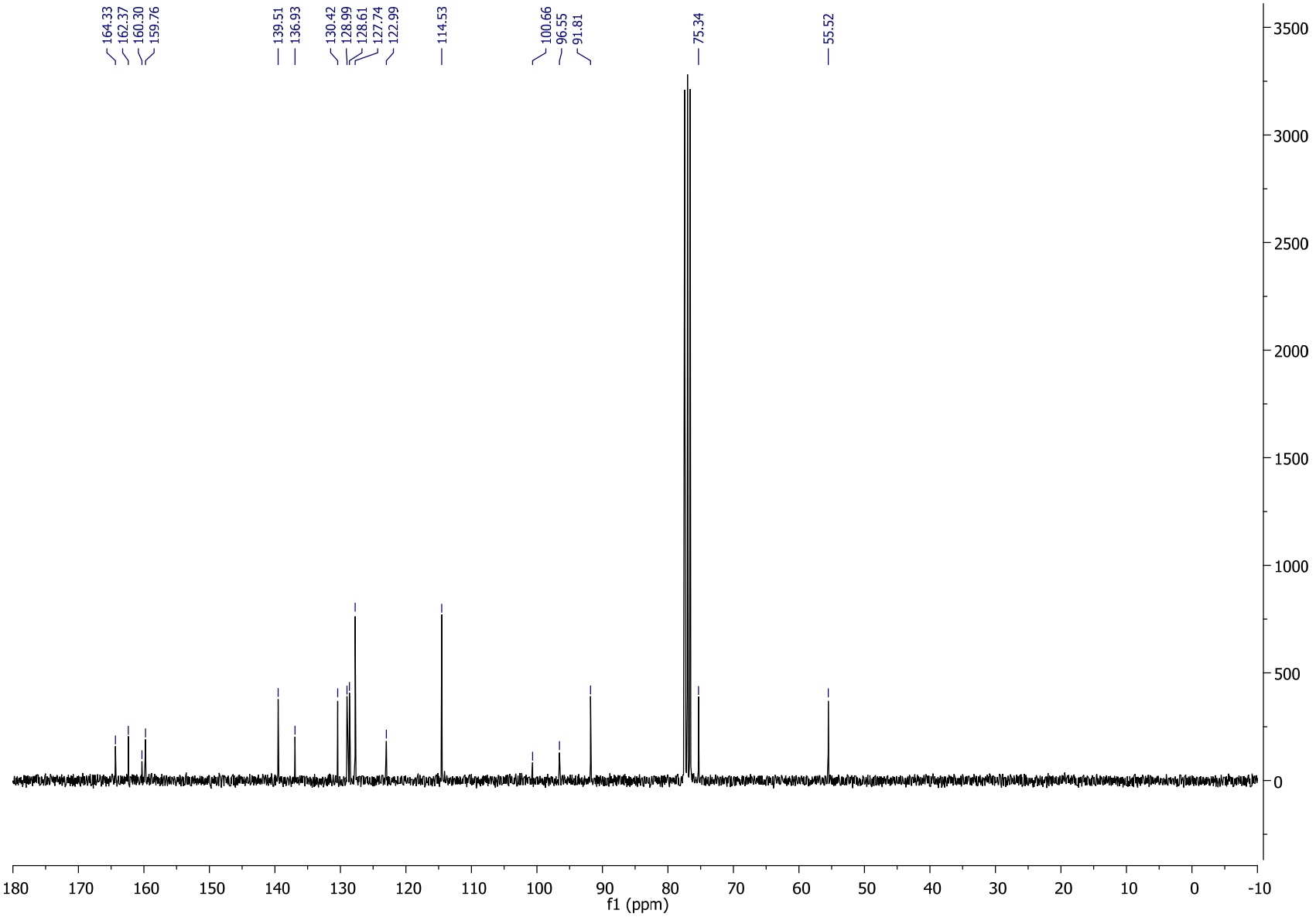
3-Chloro- 4-((2-iodobenzyl)oxy)-6-methyl-2*H*-pyran-2-one, 1c



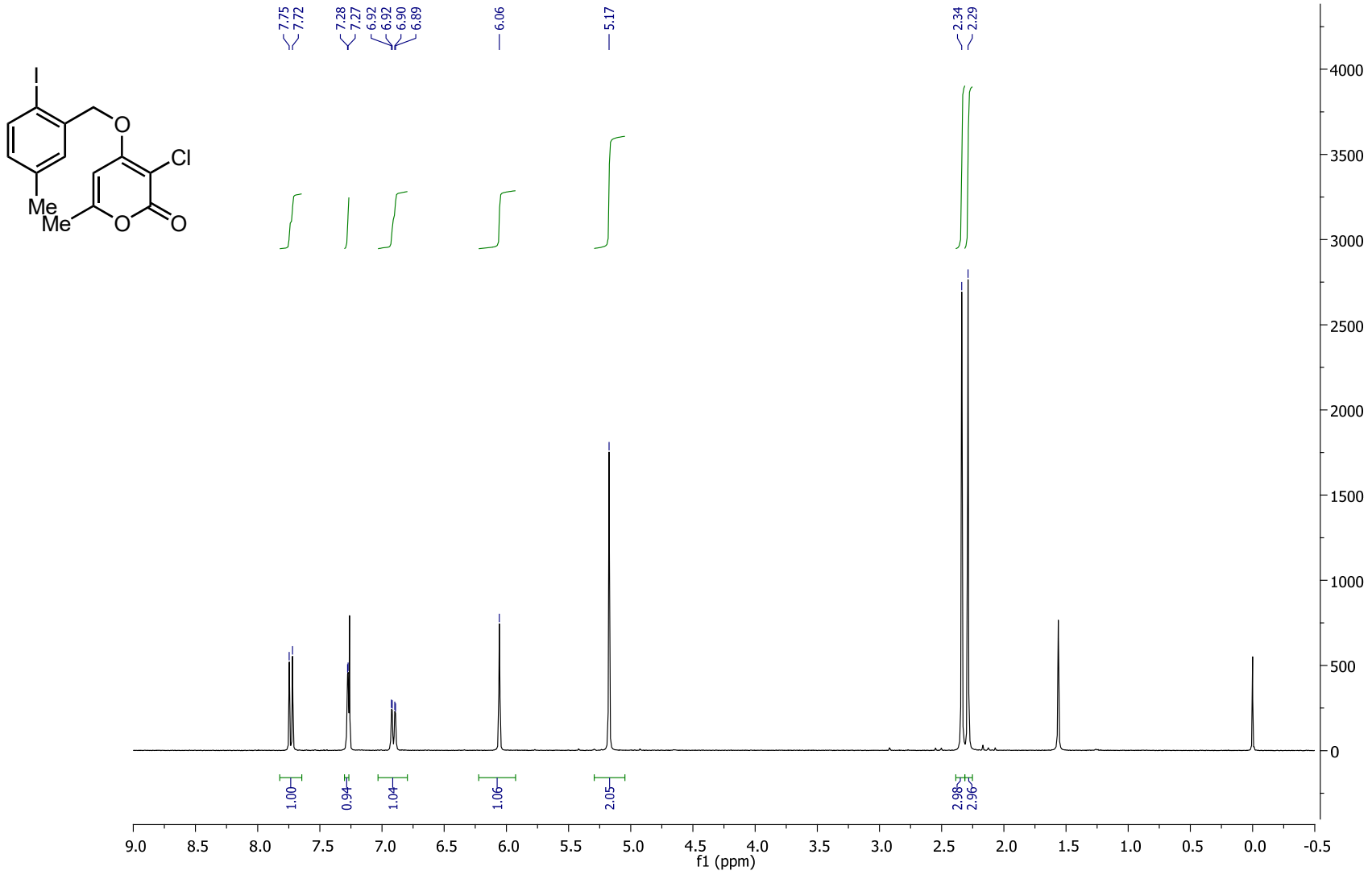

163.96
161.84
160.81
139.47
136.74
130.32
128.86
128.36
100.49
96.36
96.12
75.31
20.31
f1 (ppm)

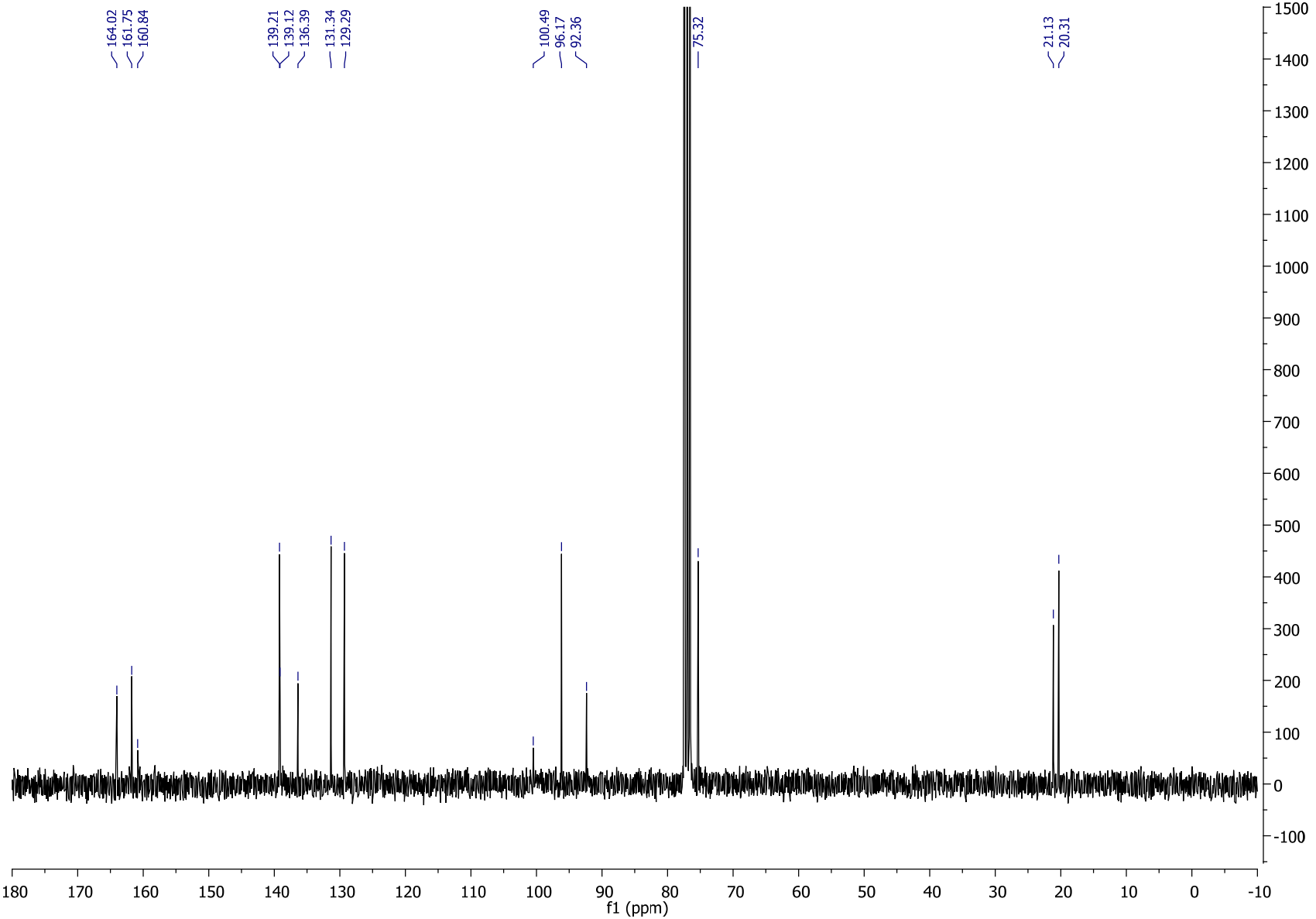
3-Chloro-4-((2-iodobenzyl)oxy)-6-(4-methoxyphenyl)-2*H*-pyran-2-one, 3



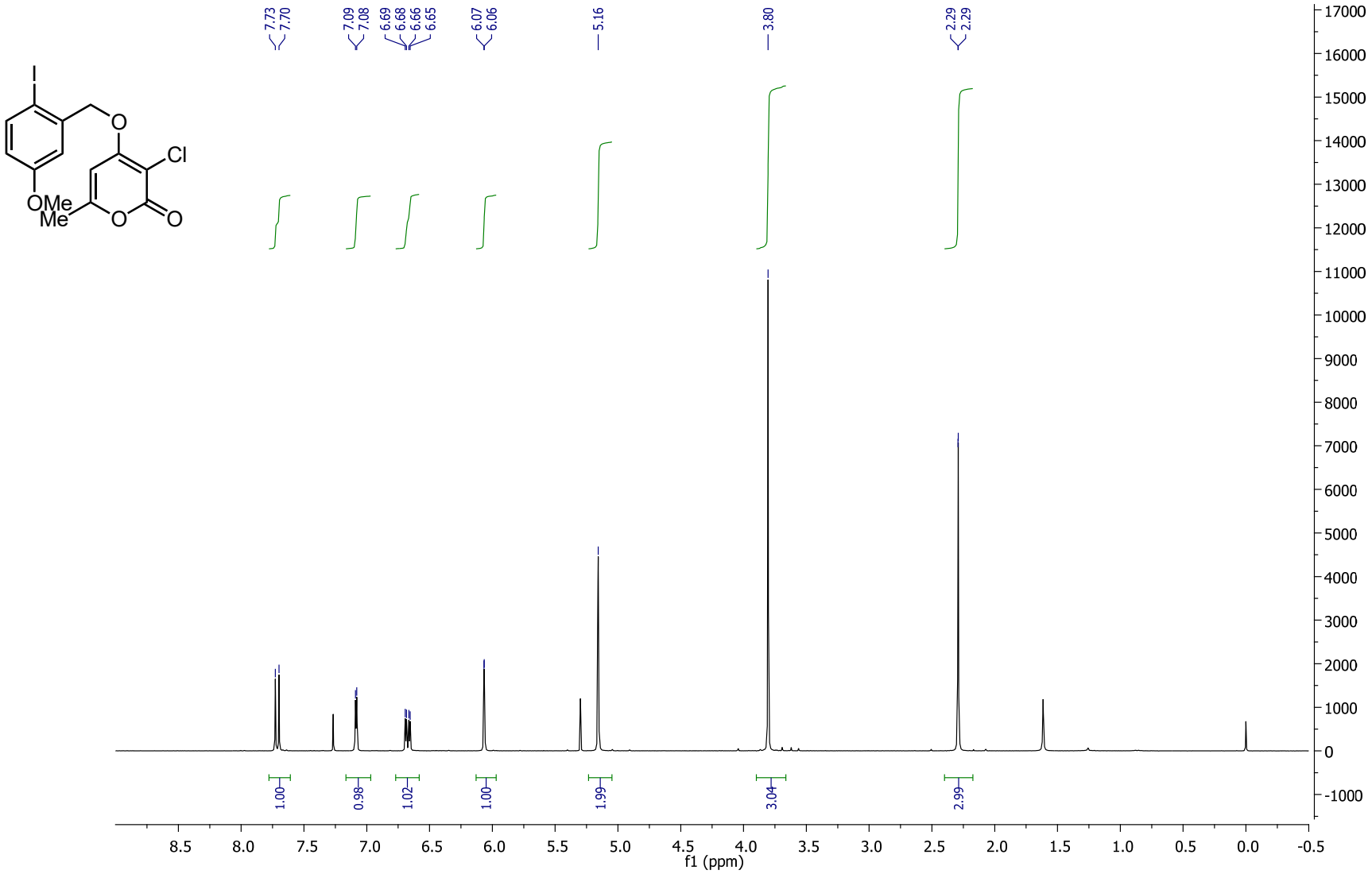

164.33
162.37
160.30
159.76
139.51
136.93
130.42
128.99
128.61
127.74
122.99
114.53
100.66
96.55
91.81
75.34
55.52
3500
3000
2500
2000
1500
1000
500
0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

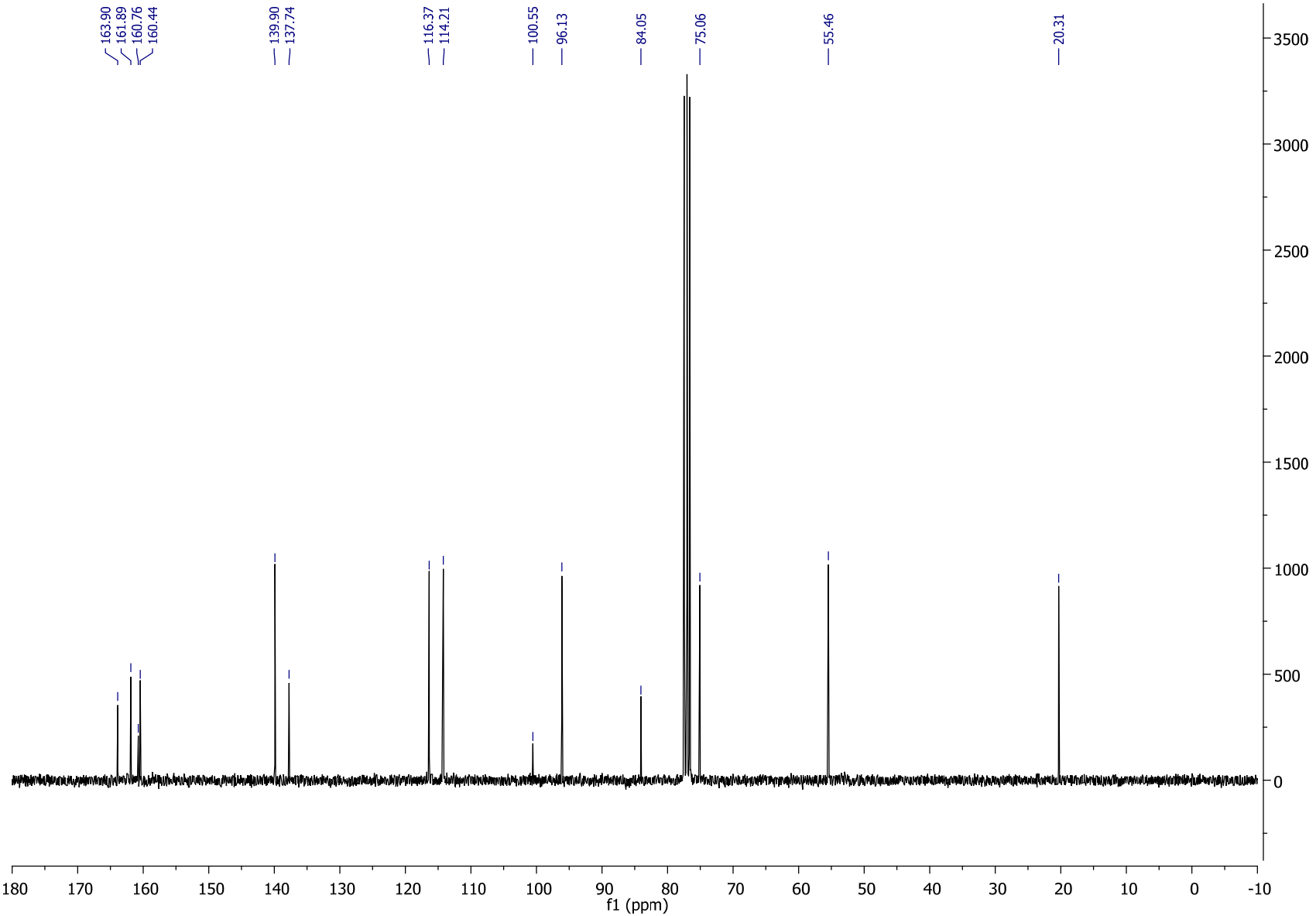
3-Chloro-4-((2-iodo-5-methylbenzyl)oxy)-6-methyl-2*H*-pyran-2-one, 4



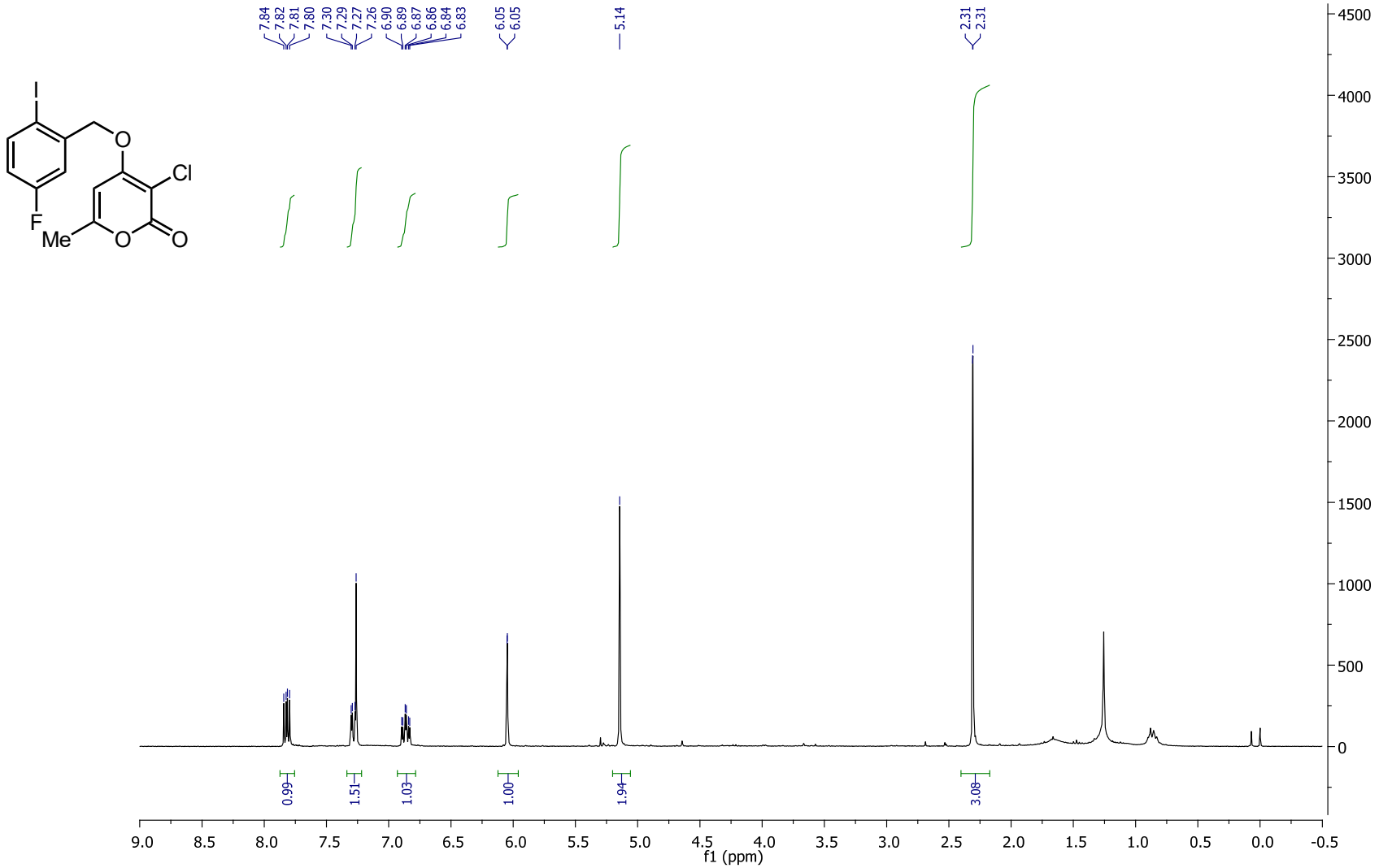

164.02
161.75
160.84
139.21
139.12
136.39
131.34
129.29
100.49
96.17
92.36
75.32
21.13
20.31
f1 (ppm)

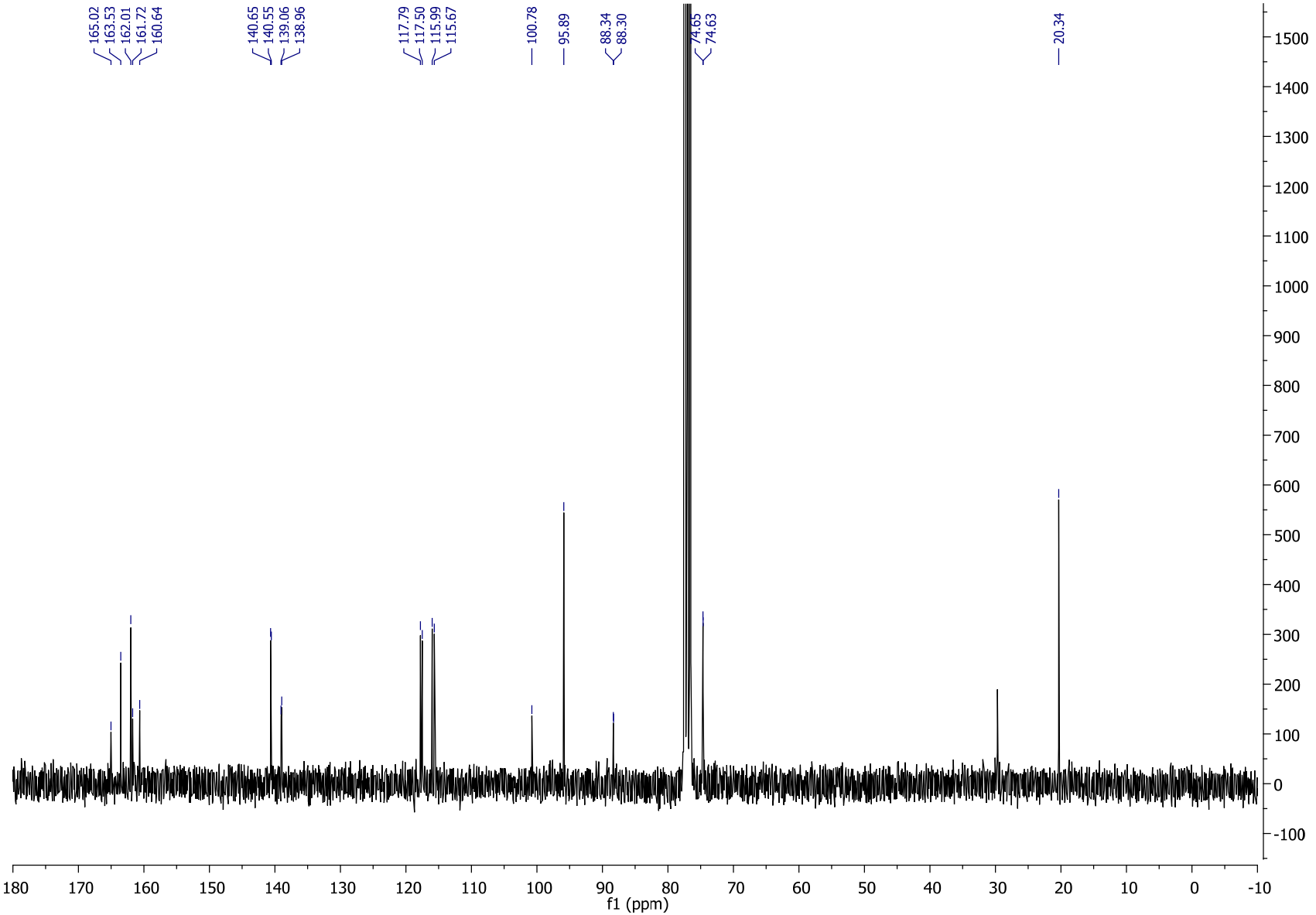
3-Chloro-4-((2-iodo-5-methylbenzyl)oxy)-6-methyl-2*H*-pyran-2-one, 5

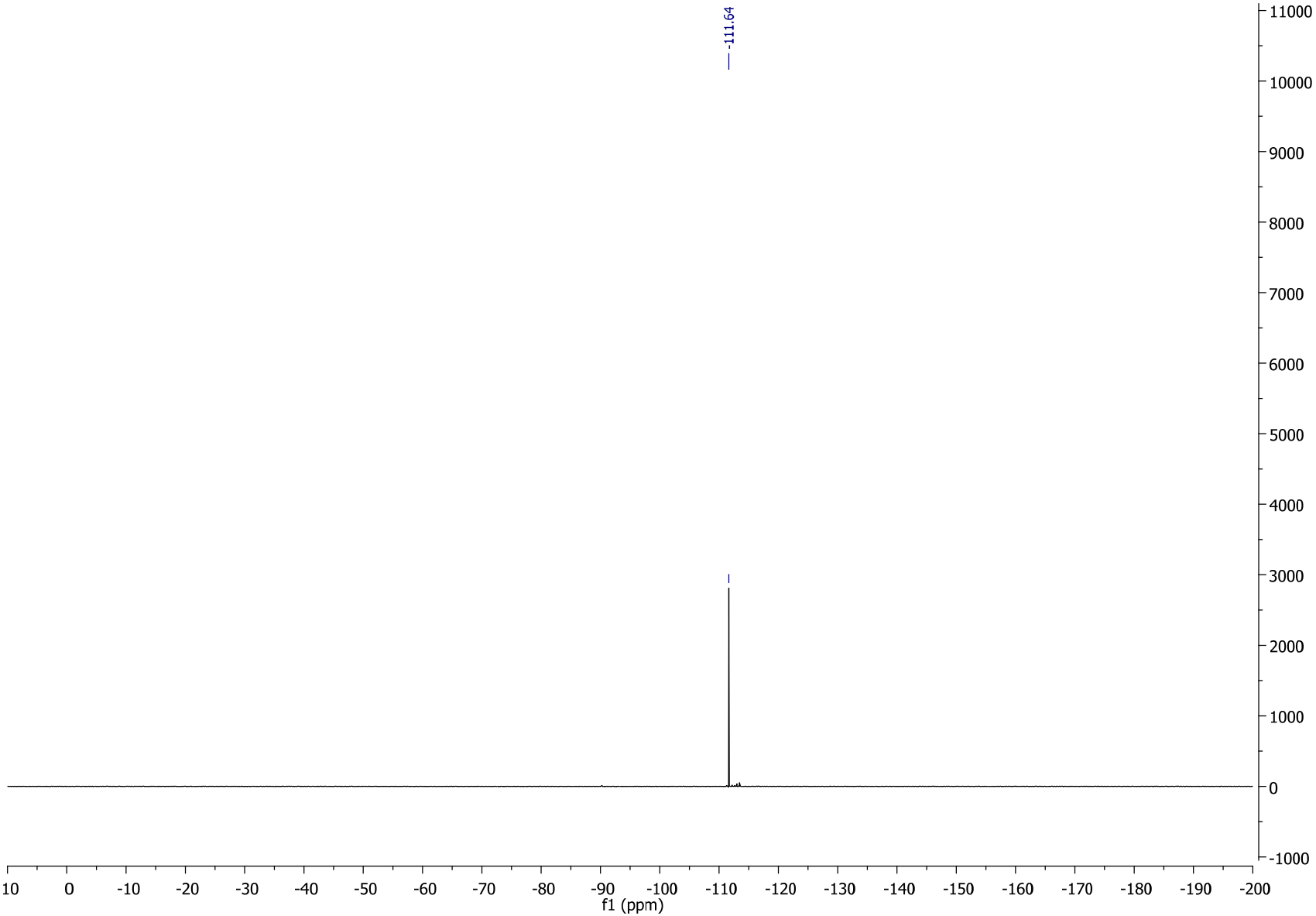



163.90
161.89
160.76
160.44
139.90
137.74
116.37
114.21
100.55
96.13
84.05
75.06
55.46
20.31
3500
3000
2500
2000
1500
1000
500
0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

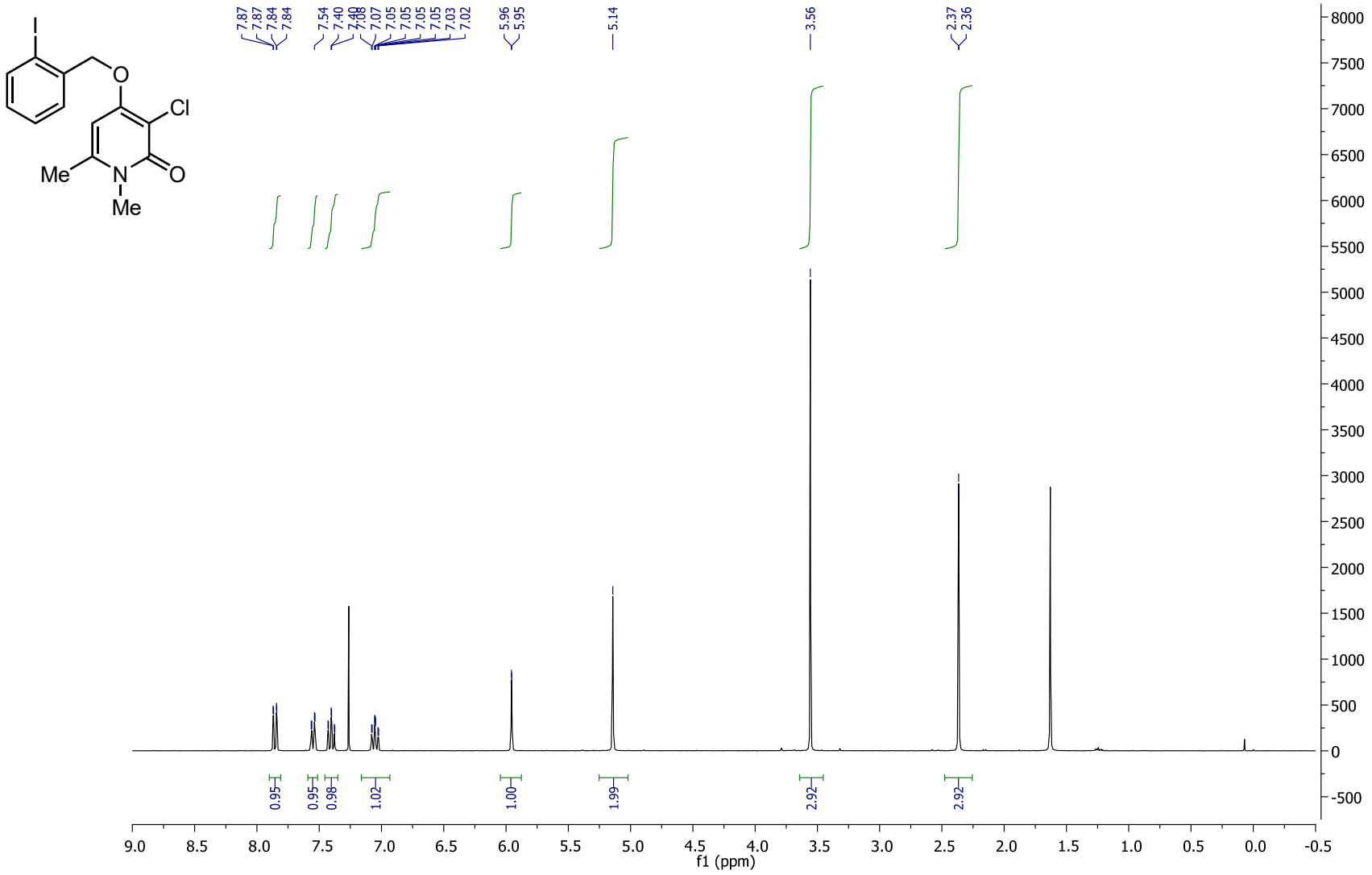
3-Chloro-4-((5-fluoro-2-iodobenzyl)oxy)-6-methyl-2*H*-pyran-2-one, 6

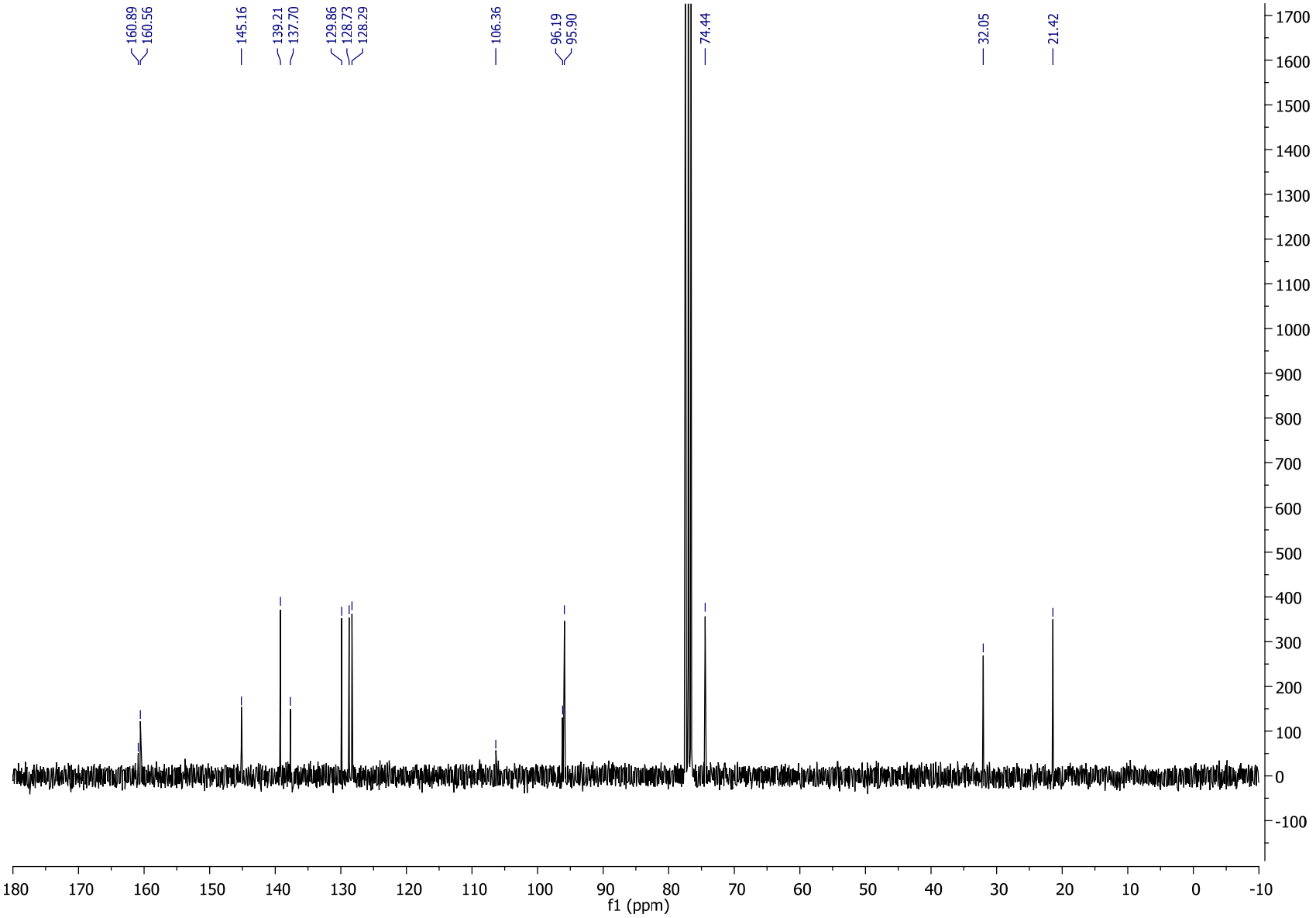



165.02
163.53
162.01
161.72
160.64
140.65
140.55
139.06
138.96
117.79
117.50
115.99
115.67
100.78
95.89
88.34
88.30
74.65
74.63
20.34
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

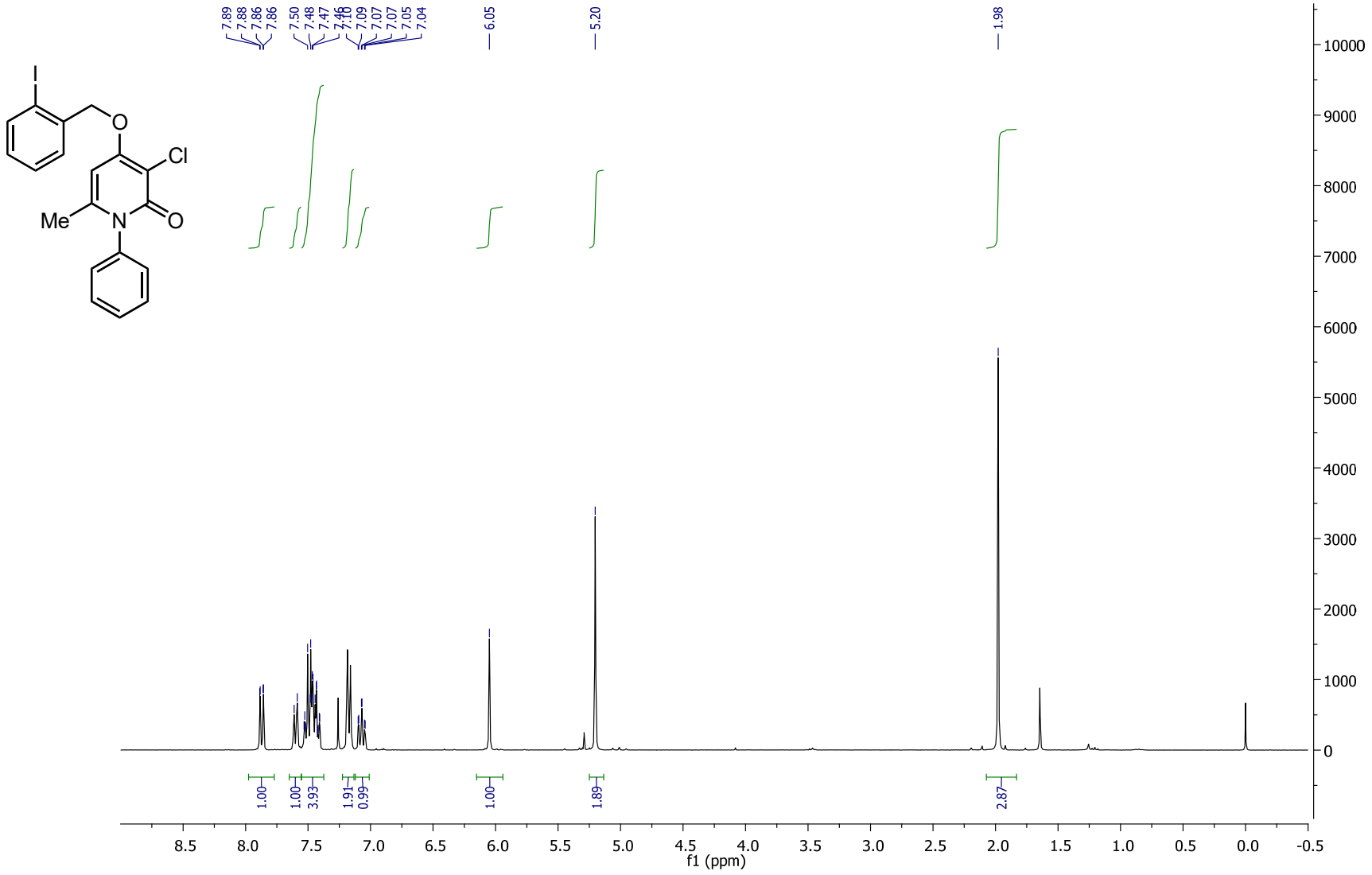

-111.64
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

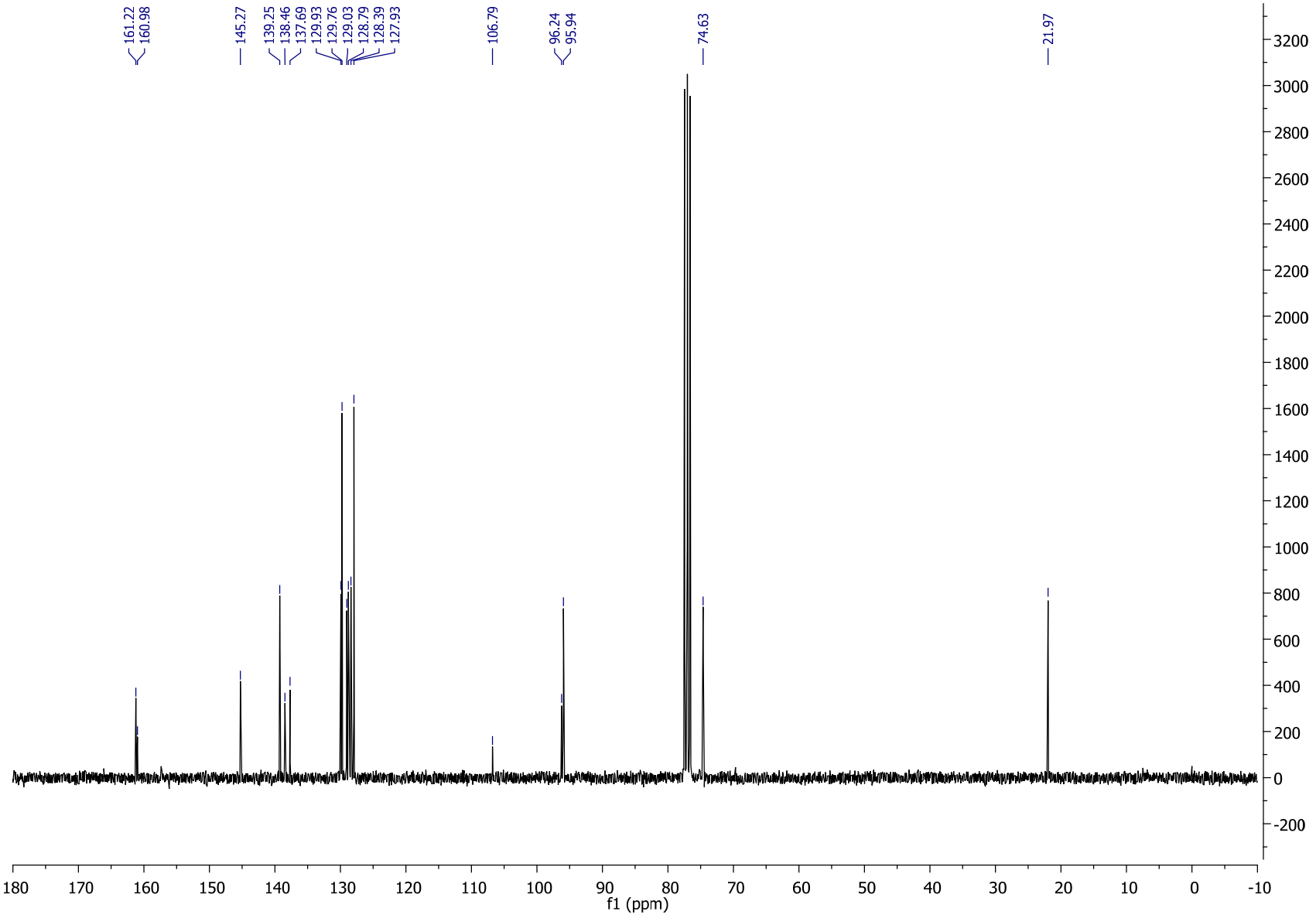
3-Chloro-4-((2-iodobenzyl)oxy)-1,6-dimethylpyridin-2(1*H*)-one, 7




160.89
160.56
145.16
139.21
137.70
129.86
128.73
128.29
106.36
96.19
95.90
74.44
32.05
21.42
f1 (ppm)

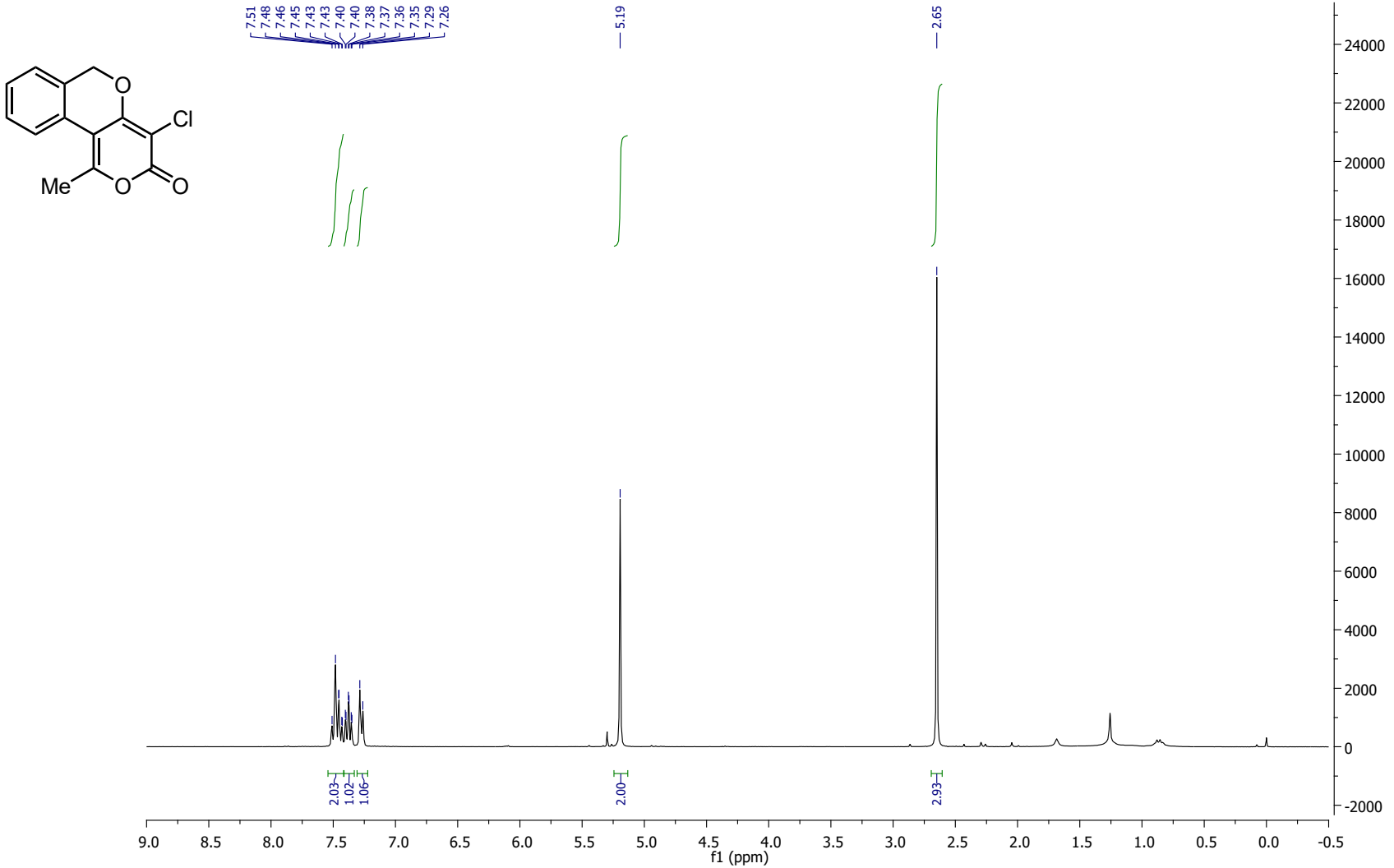
3-Chloro-4-((2-iodobenzyl)oxy)-6-methyl-1-phenylpyridin-2(1*H*)-one, 8

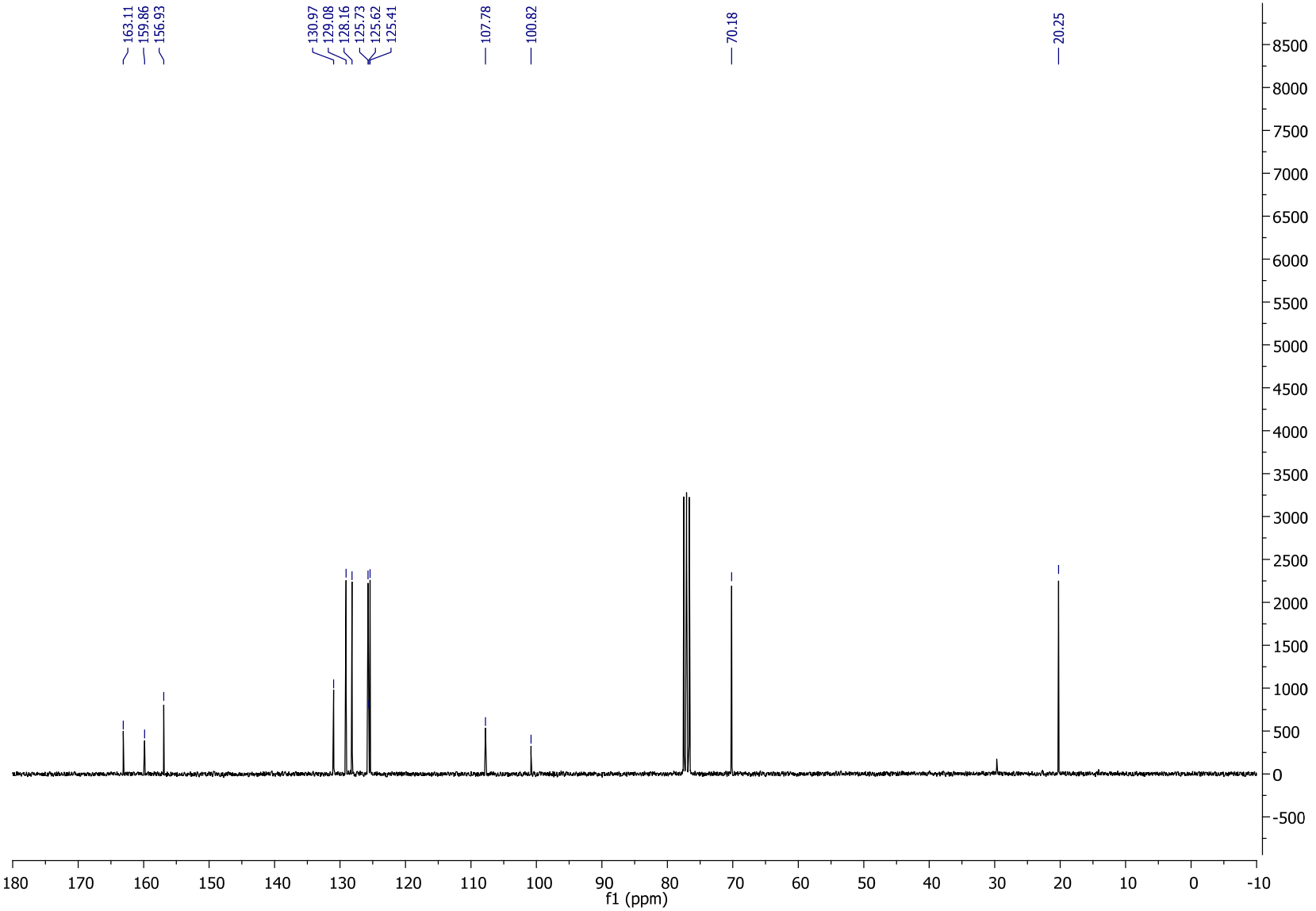



161.22
160.98
145.27
139.25
138.46
137.69
129.93
129.76
129.03
128.79
128.39
127.93
106.79
96.24
95.94
74.63
21.97
f1 (ppm)

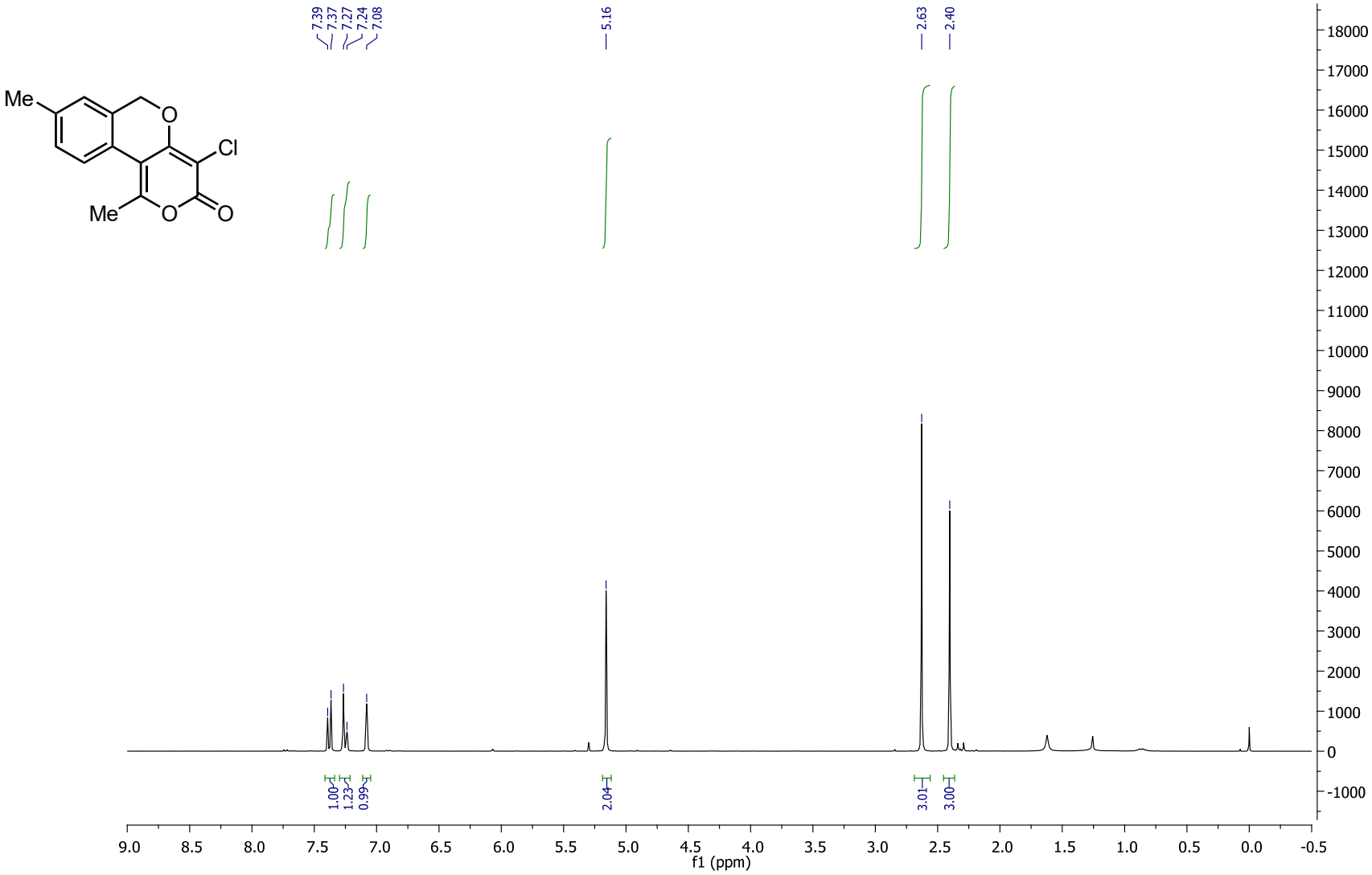
Direct Arylation Products (2c, 9-14)

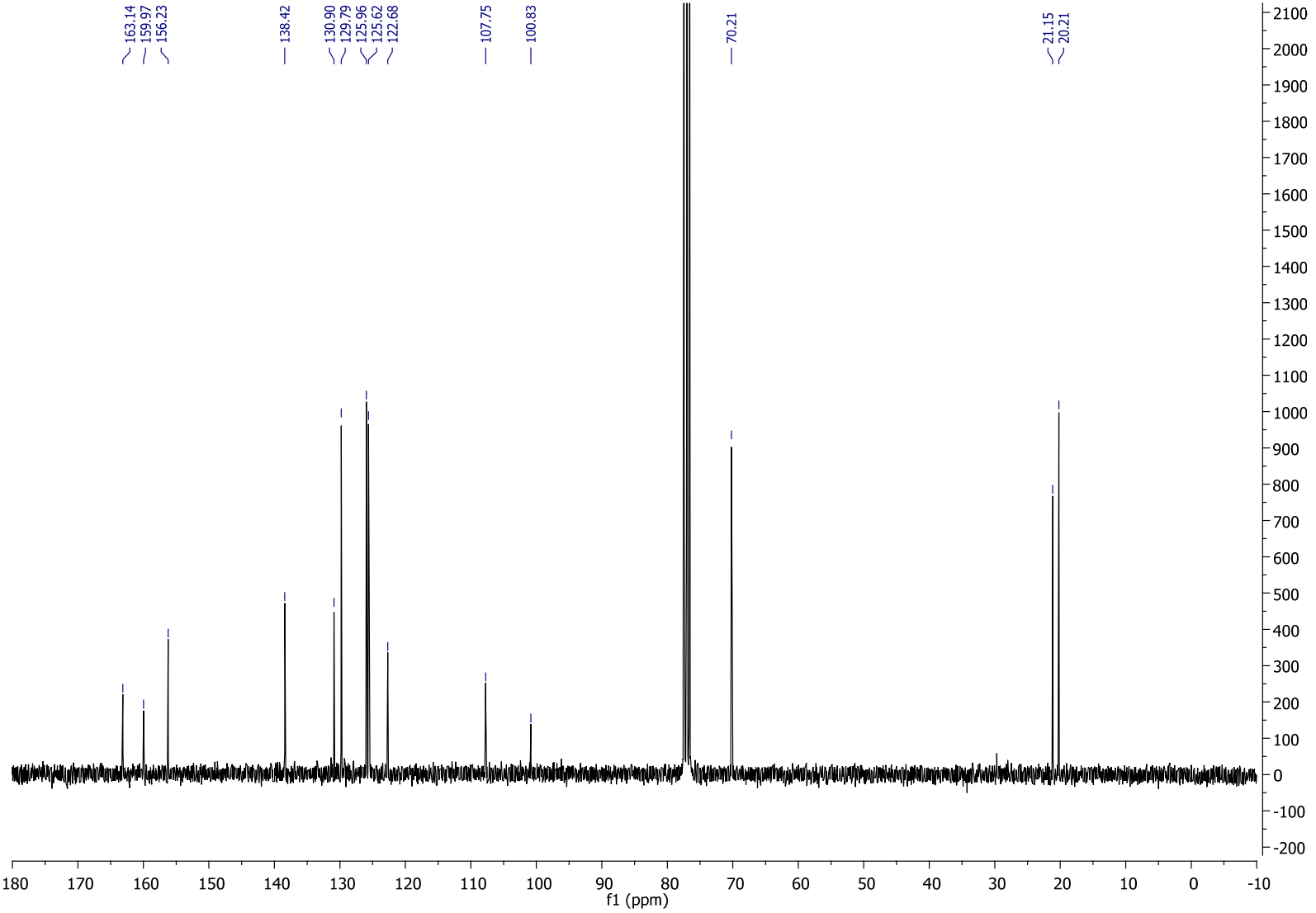
4-Chloro-1-methyl-3*H*,6*H*-pyrano[4,3-*c*]isochromen-3-one, 2c



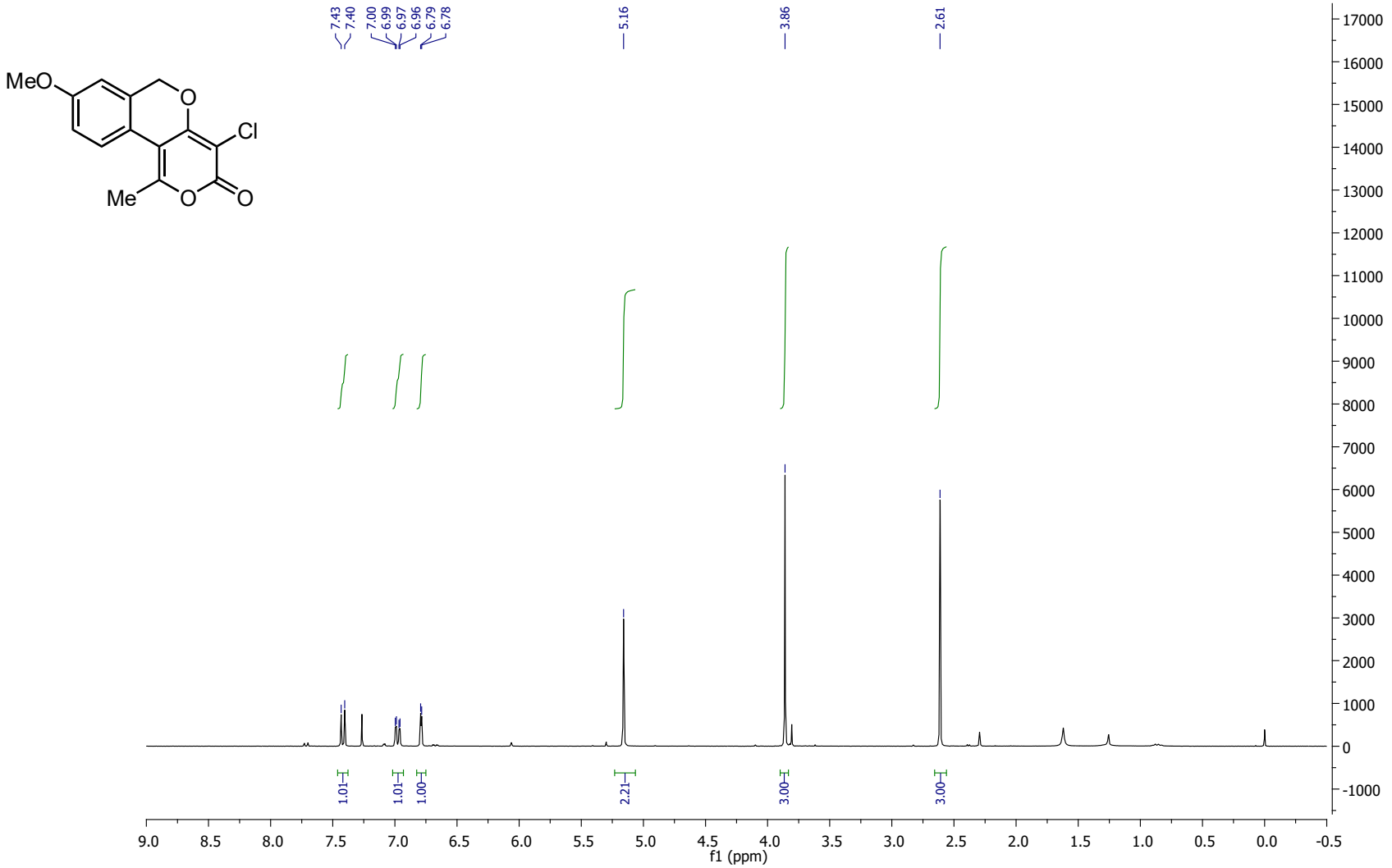

163.11
159.86
156.93
130.97
129.08
128.16
125.73
125.62
125.41
107.78
100.82
70.18
20.25
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

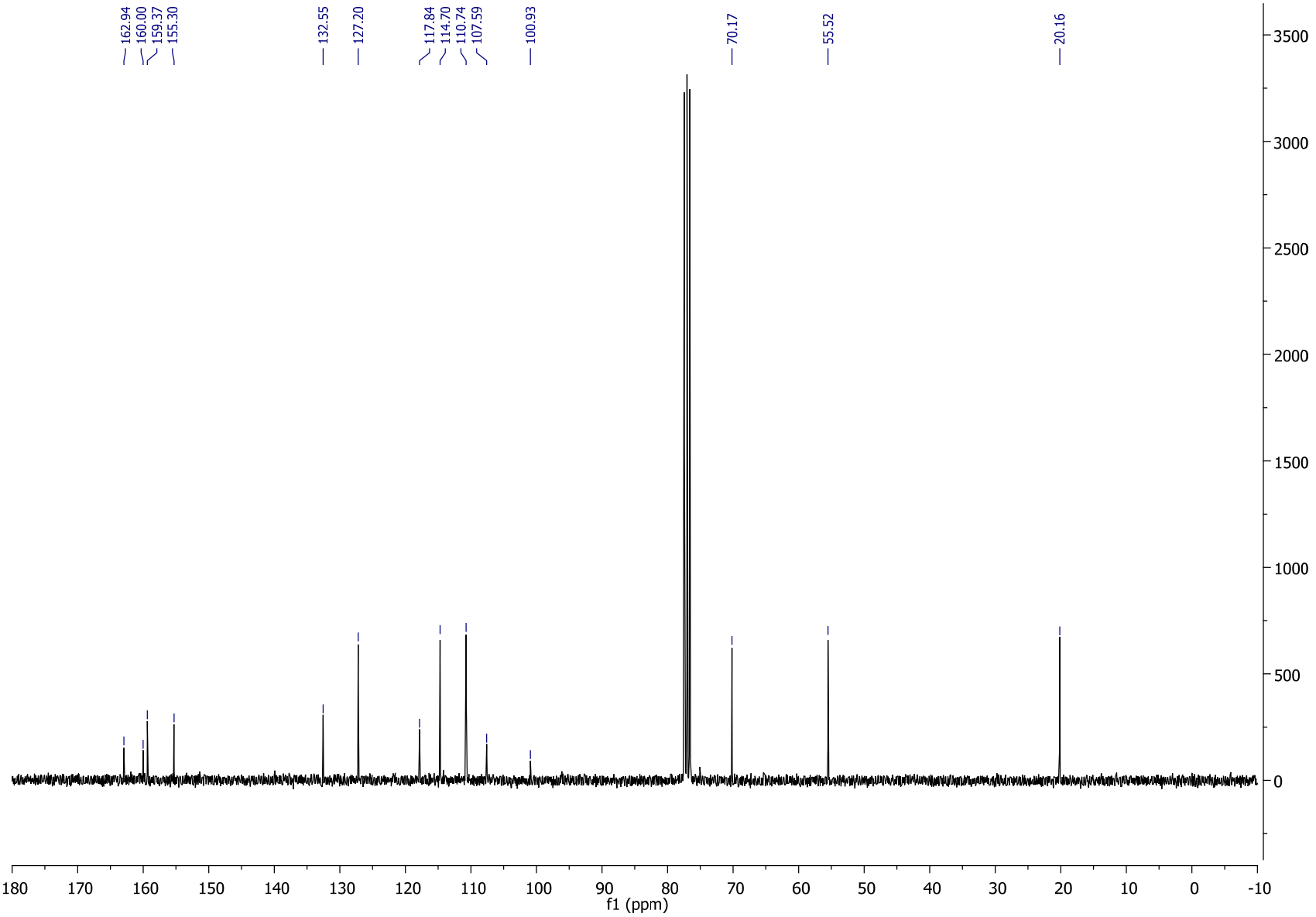
4-Chloro-1,8-dimethyl-3*H*,6*H*-pyrano[4,3-*c*]isochromen-3-one, 10



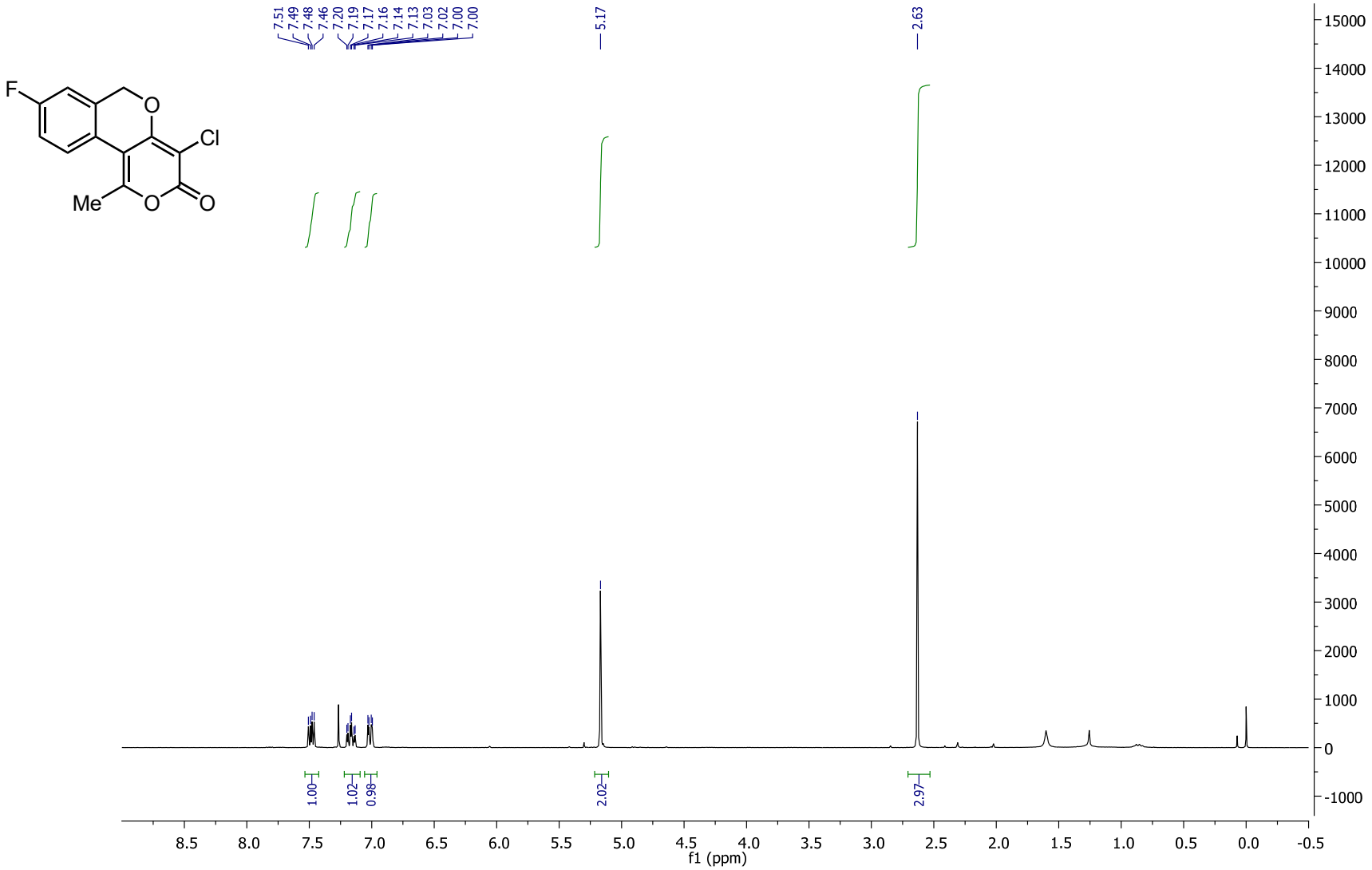

163.14
159.97
156.23
138.42
130.90
129.79
125.96
125.62
122.68
107.75
100.83
70.21
21.15
20.21
f1 (ppm)

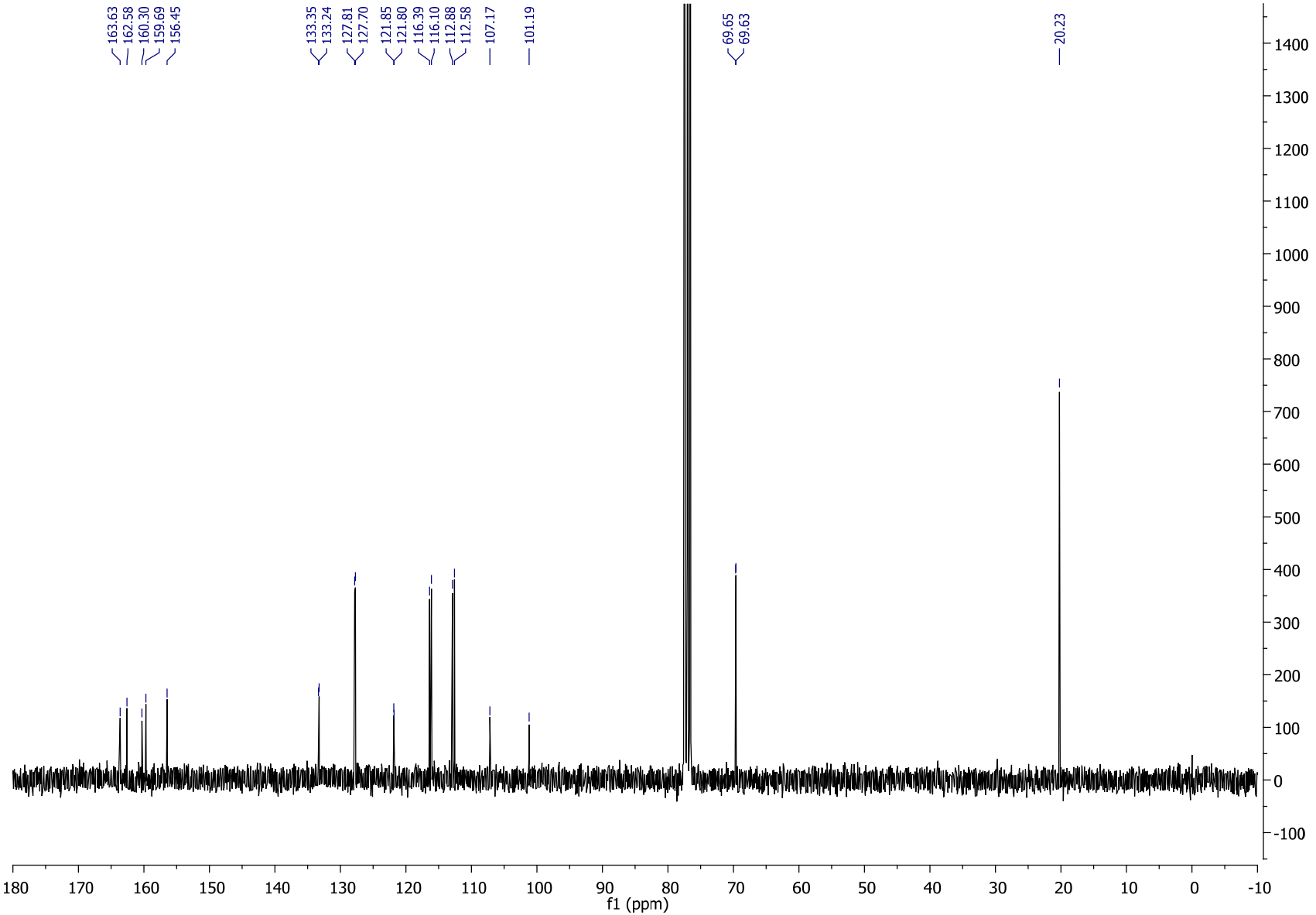
4-Chloro-8-methoxy-1-methyl-3*H*,6*H*-pyrano[4,3-*c*]isochromen-3-one, 11

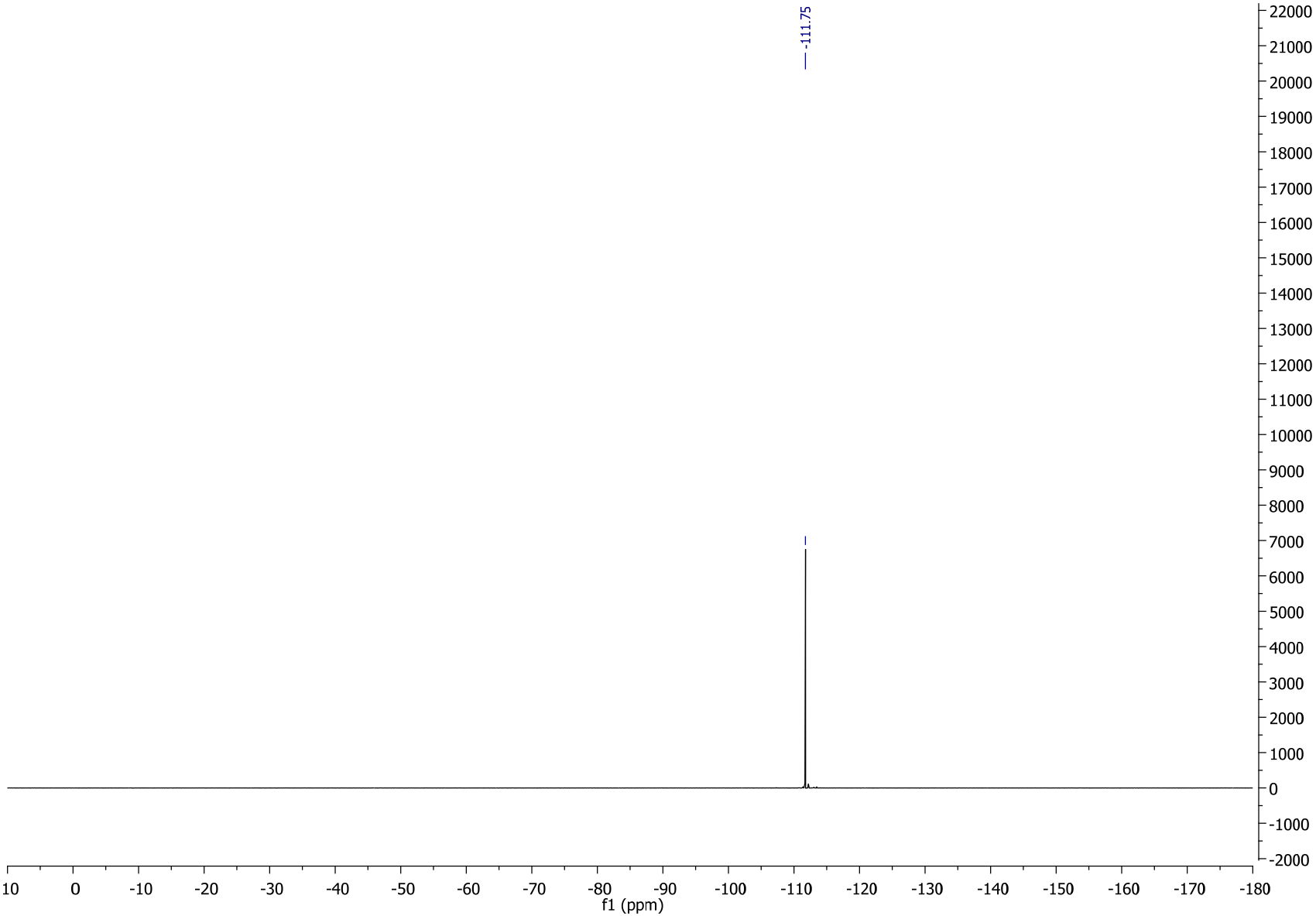



162.94
160.00
159.37
155.30
132.55
127.20
117.84
114.70
110.74
107.59
100.93
70.17
55.52
20.16
3500
3000
2500
2000
1500
1000
500
0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

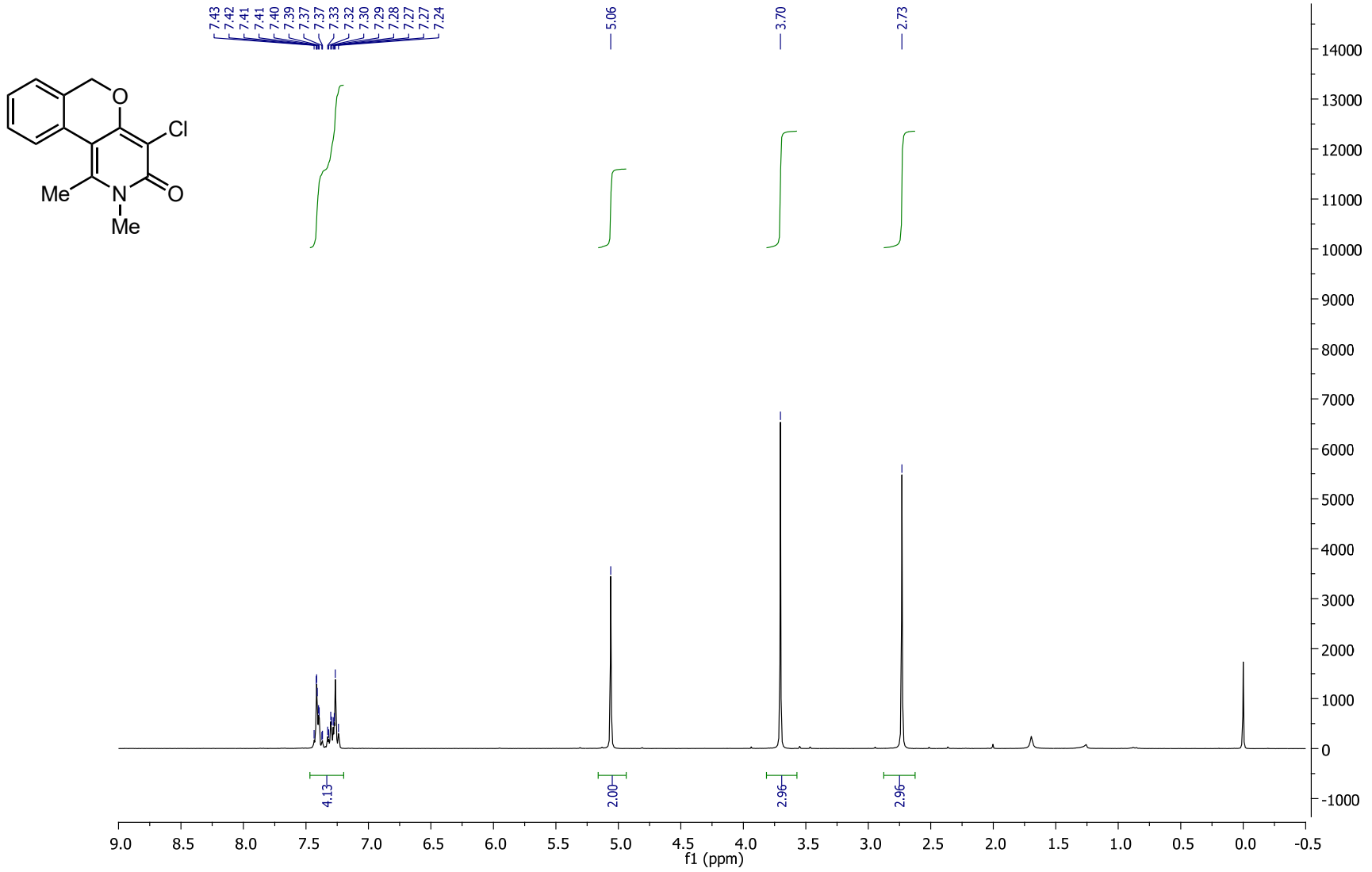
4-Chloro-8-fluoro-1-methyl-3*H*,6*H*-pyrano[4,3-*c*]isochromen-3-one, 12

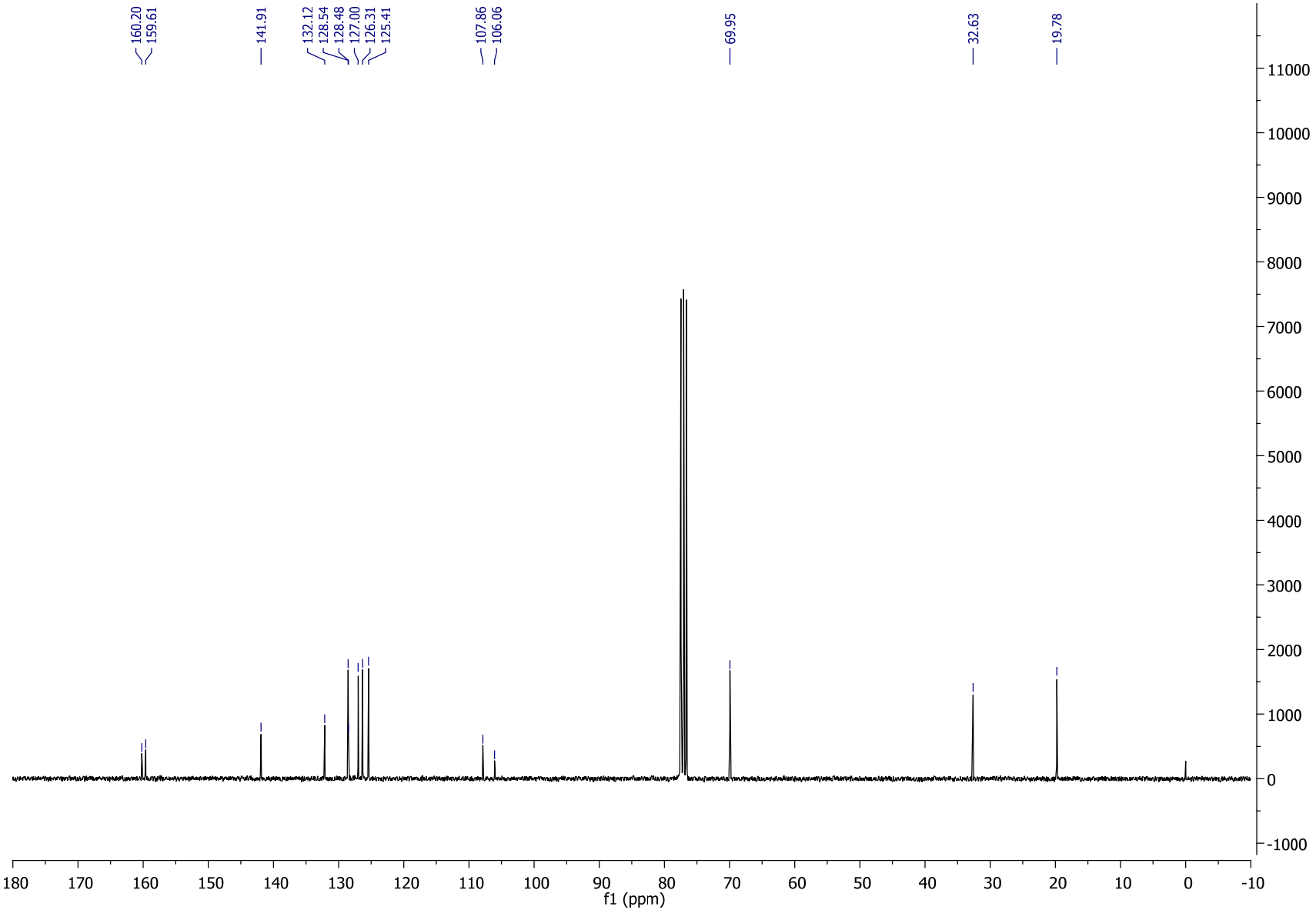



163.63
162.58
160.30
159.69
156.45
133.35
133.24
127.81
127.70
121.85
121.80
116.39
116.10
112.88
112.58
107.17
101.19
69.65
69.63
20.23
f1 (ppm)

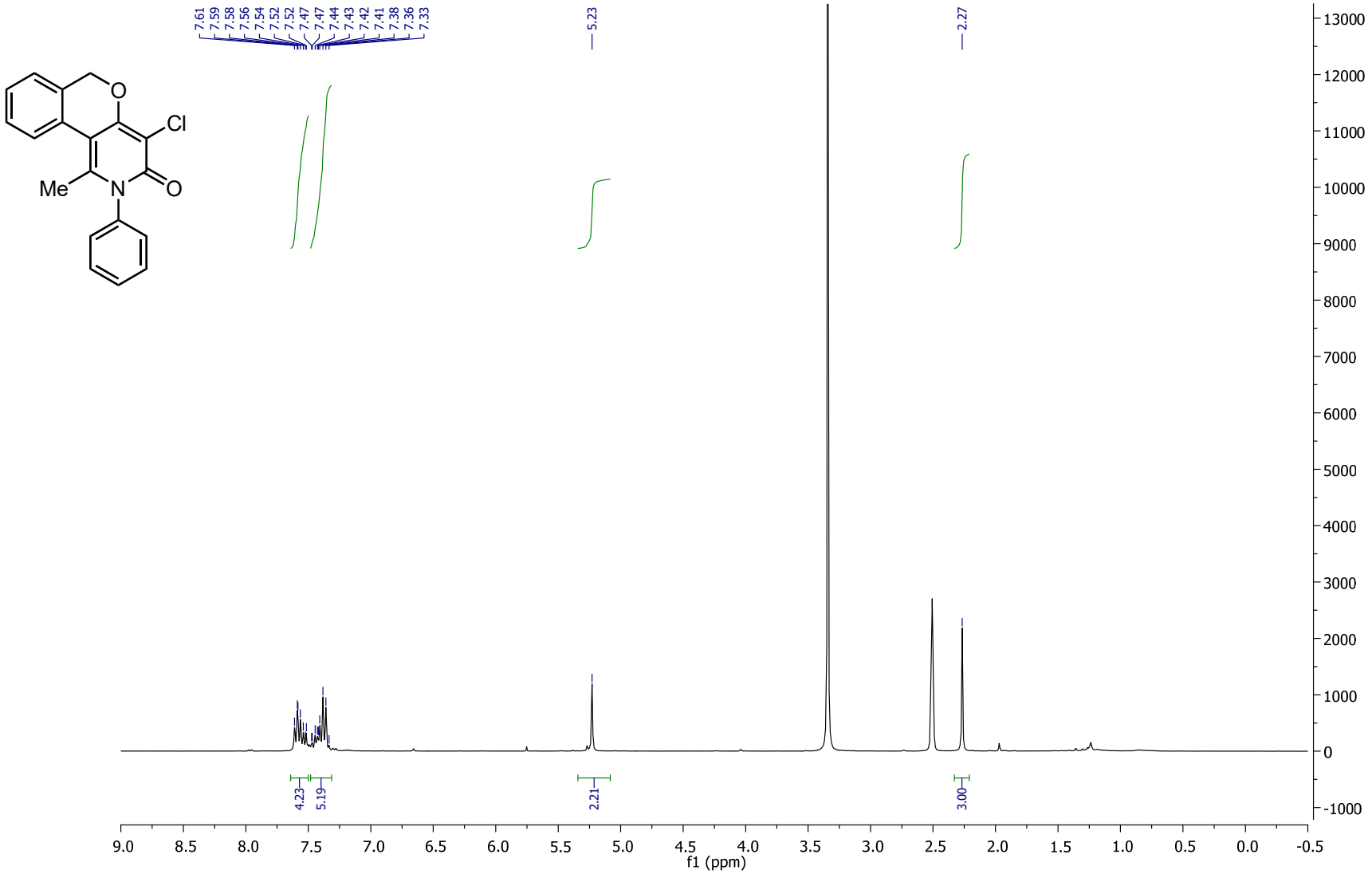

-111.75
22000
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
f1 (ppm)

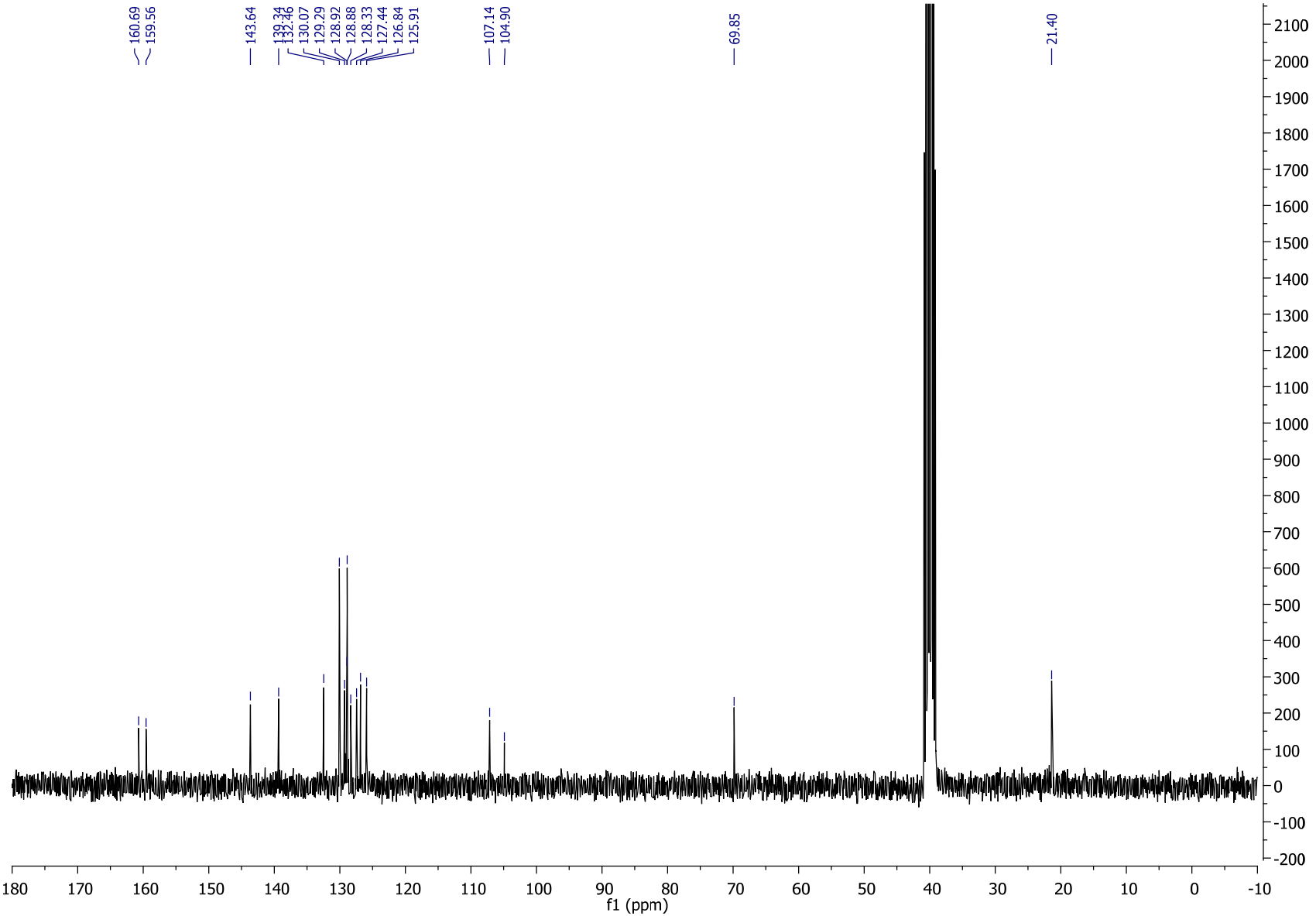
4-Chloro-1,2-dimethyl-2,6-dihydro-3*H*-isochromeno[4,3-*c*]pyridin-3-one, 13




160.20
159.61
141.91
132.12
128.54
128.48
127.00
126.31
125.41
107.86
106.06
69.95
32.63
19.78
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

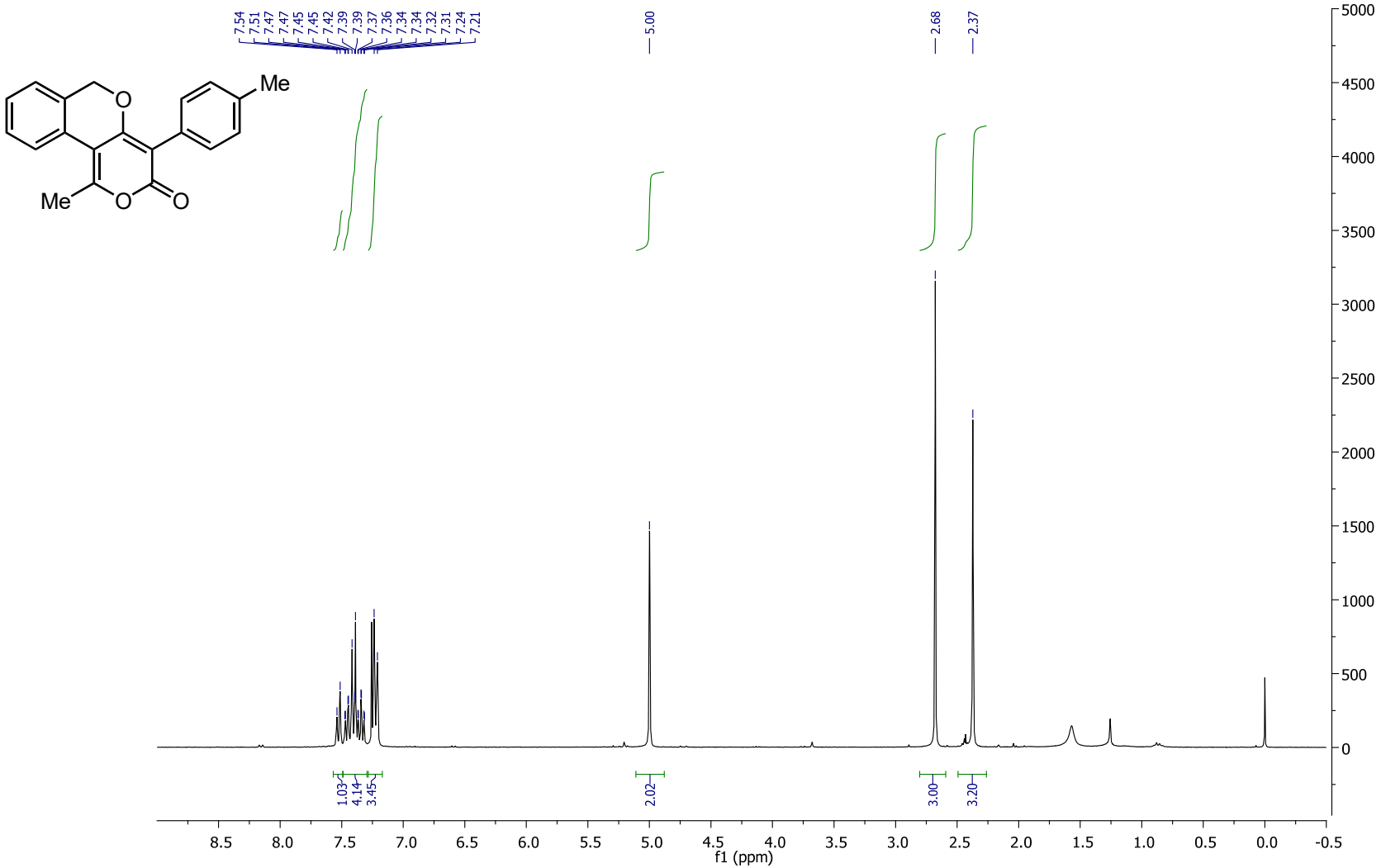
4-Chloro-1-methyl-2-phenyl-2,6-dihydro-3*H*-isochromeno[4,3-*c*]pyridin-3-one, 14

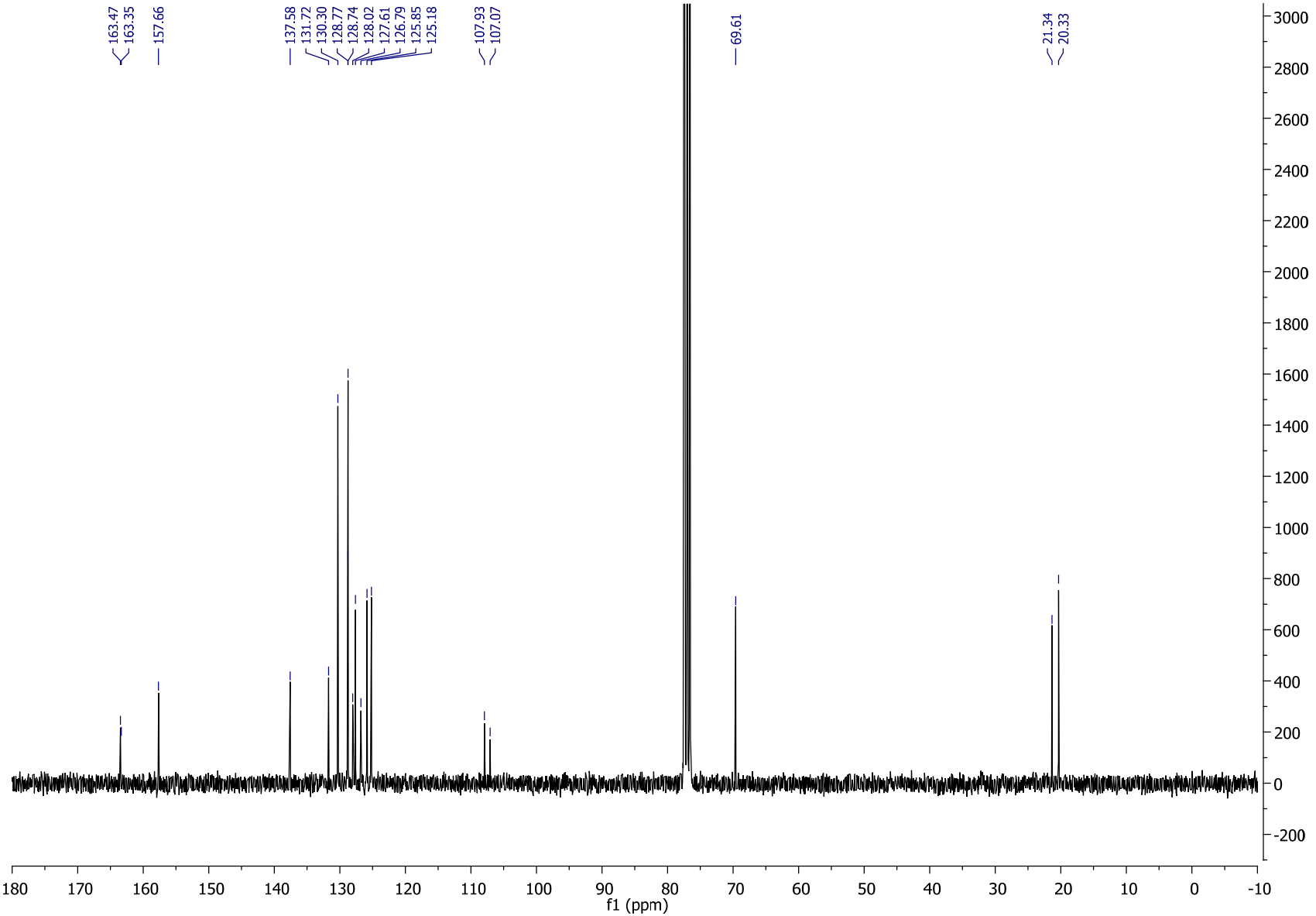



160.69
159.56
143.64
139.34
132.46
130.07
129.29
128.92
128.88
128.33
127.44
126.84
125.91
107.14
104.90
69.85
21.40
f1 (ppm)

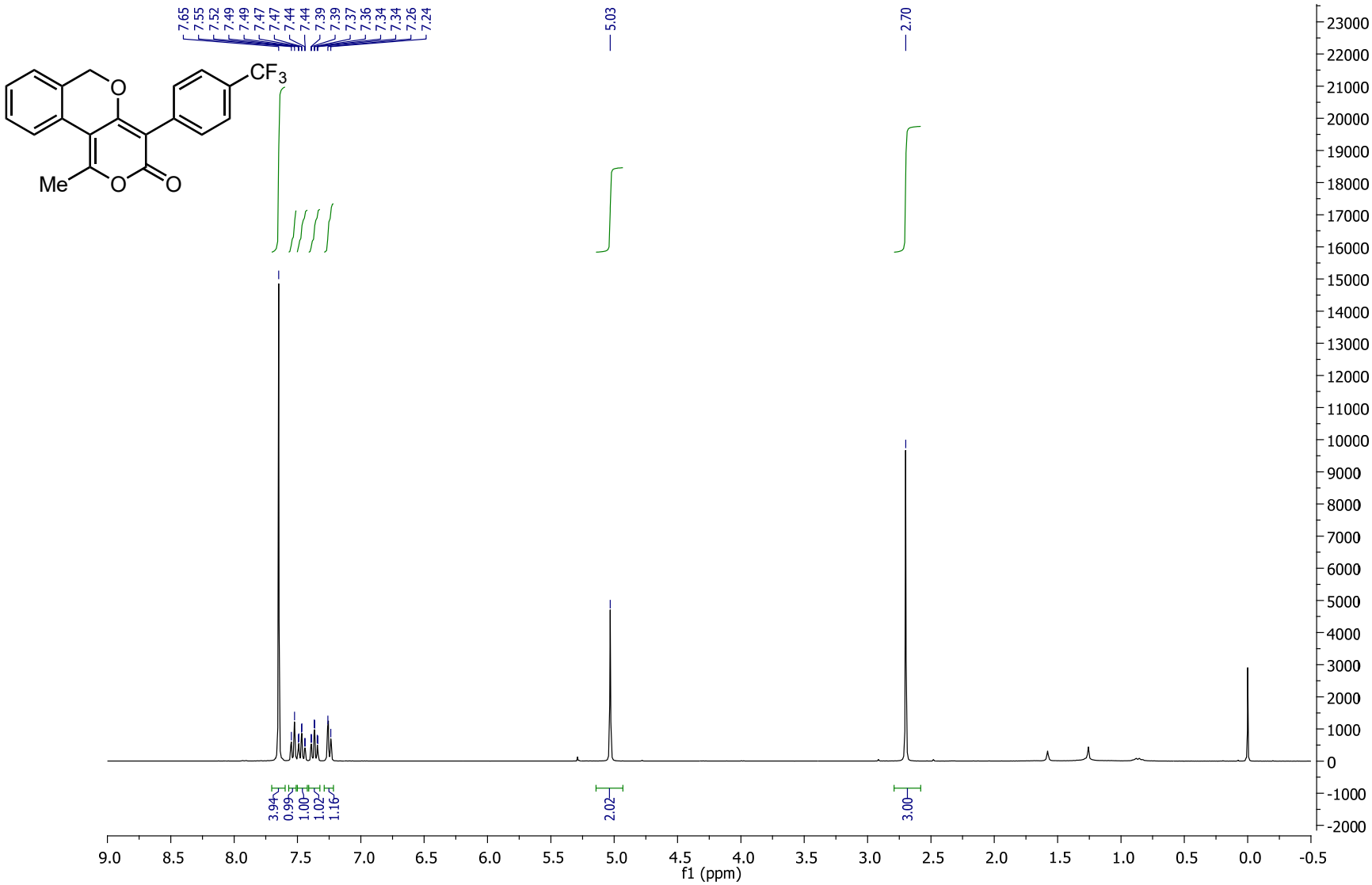
Suzuki-Miyaura Cross-Coupling Products (15-16)

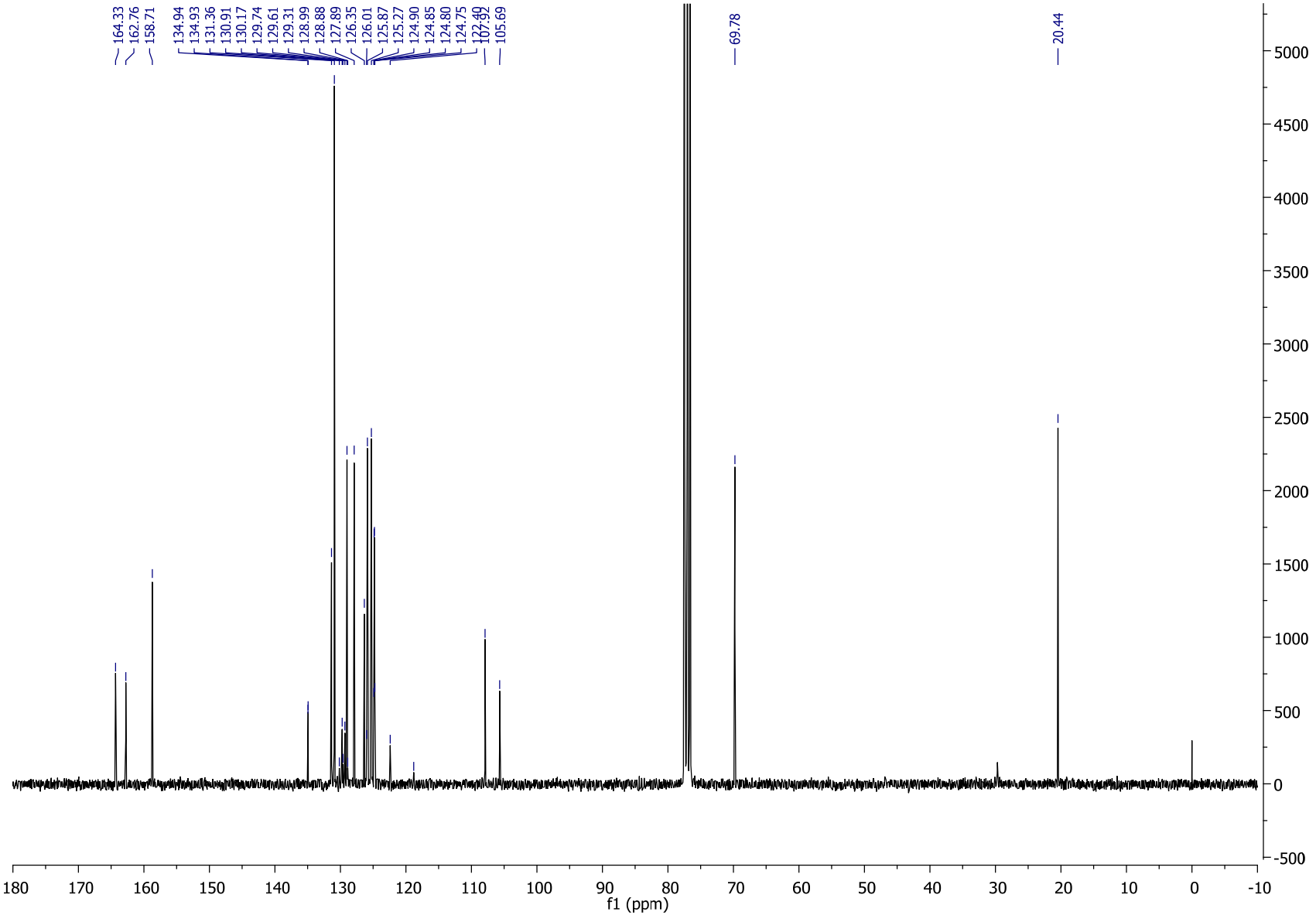
1-Methyl-4-(*p*-tolyl)-3*H*,6*H*-pyrano[4,3-*c*]isochromen-3-one, 15

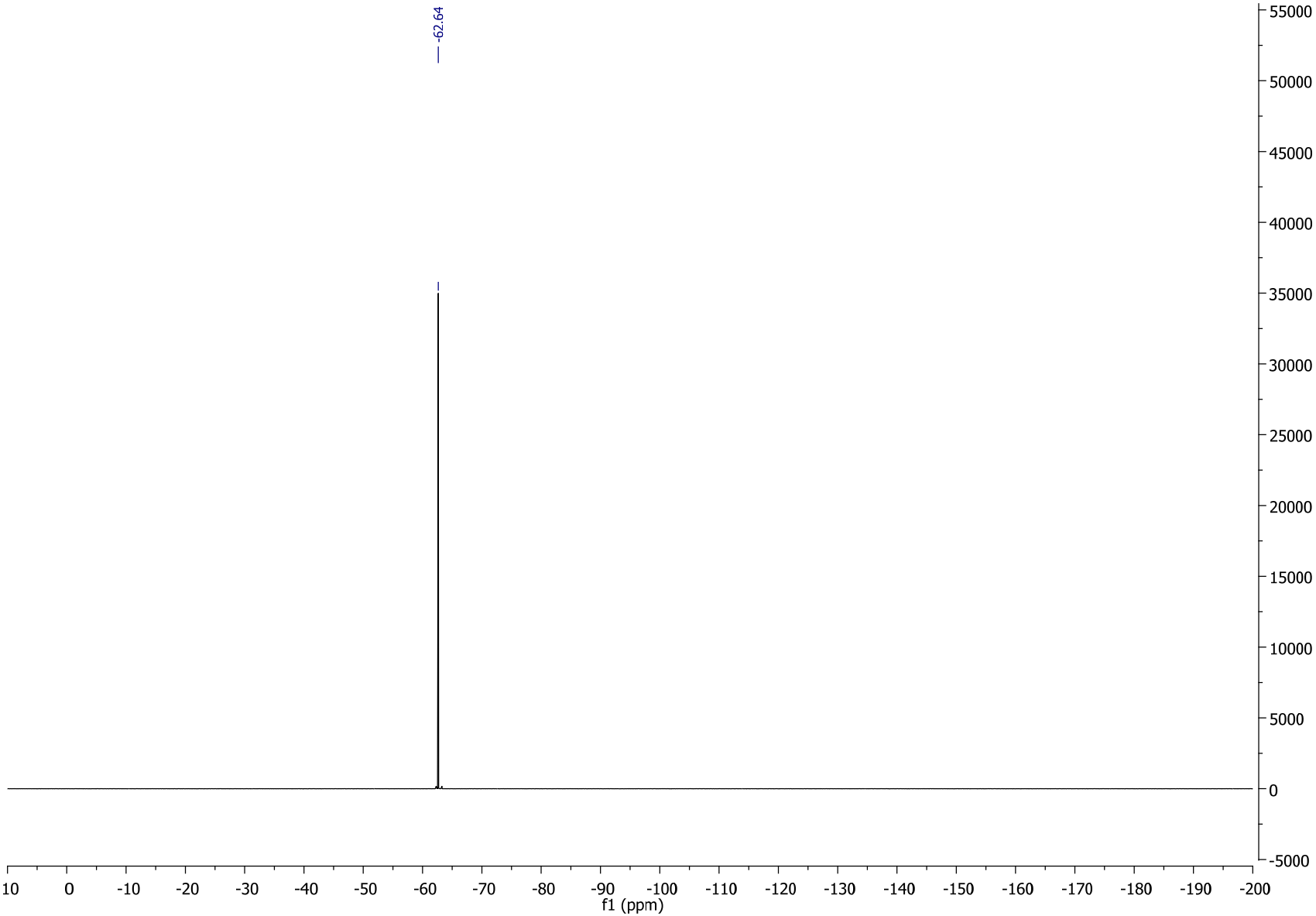



163.47
163.35
157.66
137.58
131.72
130.30
128.77
128.74
128.02
127.61
126.79
125.85
125.18
107.93
107.07
69.61
21.34
20.33
f1 (ppm)

1-Methyl-4-(4-(trifluoromethyl)phenyl)-3*H*,6*H*-pyrano[4,3-*c*]isochromen-3-one, 16




164.33
162.76
158.71
134.94
134.93
131.36
130.91
130.17
129.74
129.61
129.31
128.99
128.88
127.89
126.35
126.01
125.87
125.27
124.90
124.85
124.80
124.75
122.40
107.92
105.69
69.78
20.44
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


-62.64
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)